

**In the United States Court of Federal Claims  
OFFICE OF SPECIAL MASTERS  
No. 15-671V  
Filed: December 9, 2022**

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## RULING ON ENTITLEMENT<sup>1</sup>

### Oler, Special Master:

On June 29, 2015, John and Huali Thompson (“Petitioners”) filed a petition for compensation under the National Vaccine Injury Compensation Program, 42 U.S.C. § 300aa-10, *et seq.*<sup>2</sup> (the “Vaccine Act” or “Program”) on behalf of their son, J.T., alleging he developed injuries including global developmental delay, seizure disorder, and encephalopathy, as a result of

<sup>1</sup> This Ruling will be posted on the United States Court of Federal Claims' website, in accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 (2012). **This means the Ruling will be available to anyone with access to the internet.** As provided in 42 U.S.C. § 300aa-12(d)(4)(B), however, the parties may object to the Ruling's inclusion of certain kinds of confidential information. To do so, each party may, within 14 days, request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Otherwise, this Ruling will be available to the public in its present form. *Id.*

<sup>2</sup> National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755. Hereinafter, for ease of citation, all “§” references to the Vaccine Act will be to the pertinent subparagraph of 42 U.S.C. § 300aa (2012).

the DTaP (diphtheria, tetanus, and pertussis) and Hib (*Haemophilus influenzae* type b) vaccinations<sup>3</sup> he received on July 7, 2012. Pet. at 1, ECF No. 1.

Upon review of the evidence, I find that Petitioners have preponderantly demonstrated that the Pentacel vaccine J.T. received caused a significant aggravation of his previously asymptomatic Dravet syndrome. Petitioners are entitled to compensation.

## I. Procedural History

Petitioners filed their petition on June 29, 2015. ECF No. 1 (“Pet.”). Petitioners filed initial medical records on August 7, 2015.<sup>4</sup> They continued to file medical records through 2016, 2017, 2019 and 2020.

The parties then filed expert reports from several medical experts, to include Dr. Yuval Shafrir (Exs. 45, 101, 114, 146), Dr. Michael Kohrman (Exs. A, C, L), Dr. Gerald Raymond (Exs. D, J), and Dr. Andrew MacGinnitie (Ex. G).

I conducted an entitlement hearing on September 23-24, 2020 where I heard testimony from Mr. Thompson, Dr. Shafrir, Dr. MacGinnitie, and Dr. Raymond. See Minute Entry dated September 29, 2020. Over the next nine months, the parties filed post-hearing briefs. Pet’r’s Post Hearing Brief; ECF No. 138; Respt’s Post Hearing Brief; ECF No. 140; Pet’r’s Reply Brief; ECF No. 141. This matter is ripe for an adjudication.

## II. Medical Records

J.T. was born on December 31, 2011, after an uncomplicated pregnancy. Ex. 28 at 19. He received vaccinations shortly after birth, and at ages two months and four months and suffered no complications. Ex. 2 at 1, 8, 11. At his four-month well child check-up, J.T.’s pediatrician, Dr. Fleischer, remarked that J.T. was “sociable, vocal, [and had] good head control” and that he “grabs.” *Id.* at 11. Aside from a brief hospitalization for croup at age four months, J.T.’s medical history before vaccination was unremarkable. *Id.*

On July 7, 2012, J.T. returned to Dr. Fleischer for his six-month well child check-up, at which time he received the Pentacel, PCV13, and Rotateq vaccinations. Ex. 2 at 12. His physical and developmental exams were normal. *Id.* Between 8:00 and 9:00 p.m. that night, Petitioner Huali Thompson (hereinafter “Ms. Thompson”) heard “a cry” from J.T. and found him in a “tonic rigid state” which lasted for two minutes, “followed by a period of being flaccid,” which lasted for five minutes. Ex. 1 at 13, 43. Ms. Thompson called 911 and the paramedics found J.T. “quiet,” but “in no distress.” Ex. 5 at 5. He was able to “look[] about and focus[] on the person speaking.” *Id.* J.T.

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<sup>3</sup> Petitioners later specified that the Pentacel, PCV13, and Rotateq vaccinations J.T. received on July 7, 2012 “caused an immune mediated reaction resulting in the development of an epileptic encephalopathy”. Pet’r’s Pre-Hearing Br. at 21, ECF No. 106. The Pentacel vaccine consists of DTaP, IPV, and Hib components. See <https://www.cdc.gov/vaccines/vpd/dtap-tdap-td/hcp/about-vaccine.html> (Last accessed December 8, 2022).

<sup>4</sup> These records were stricken by Special Master Gowen’s June 9, 2016 Order. ECF No. 55.

remained alert in the ambulance and his breathing was “shallow, but not labored.” *Id.* Paramedics did not take J.T.’s temperature but noted that it was normal to the touch. *Id.* at 4. On arrival at St. Luke’s Hospital, J.T. was “now back to baseline.” Ex. 1 at 43. He had a fever of 102.7 degrees Fahrenheit (39.3 degrees Celsius). *Id.* at 14, 47. The emergency room physician diagnosed a febrile seizure “[f]ollowing vaccines today.” *Id.* at 14.

On July 8, 2012, J.T. saw David Callahan, MD, for a neurology consultation following his hospitalization. Ex. 1 at 27-28. Dr. Callahan noted that J.T.’s “development has been normal,” and he concluded that J.T.’s “neurologic examination is normal” without need for further testing. *Id.* Dr. Callahan noted that J.T. had likely experienced a brief febrile or syncopal seizure the night before, but that seizure had not recurred. *Id.* at 28.

On August 31, 2012, J.T. returned to Dr. Fleischer for a developmental screening exam because Petitioners were concerned about his development. Ex. 2 at 13. Dr. Fleischer noted that J.T. was alert and vocal, but not babbling, that he would roll, but not sit alone, and did not crawl. *Id.* He further noted that J.T. did not finger feed. *Id.* Dr. Fleischer informed Petitioners that J.T. met his developmental expectations for this age, but that he would monitor J.T. *Id.*

On September 11, 2012, J.T. presented in the emergency room having exhibited two back-to-back “episodes of limpness,” each lasting 30 to 60 seconds, during which his eyes “deviated to the right.” Ex. 4 at 93. J.T. vomited after each episode. *Id.* J.T. had been experiencing nasal congestion for the previous 24 to 48 hours. *Id.* J.T. had no fever and his lab tests were unremarkable. *Id.* at 93-98. The emergency physician diagnosed an afebrile seizure and noted that “serious bacterial or viral infection is unlikely.” *Id.* at 94. A few hours later, Petitioners brought J.T. back to the emergency room with a fever of 101.5 degrees Fahrenheit and rhinorrhea. *Id.* at 108-19. The emergency room physician noted that J.T. had most likely had a febrile seizure the night before, although no fever had been identified, and that J.T.’s fever and rhinorrhea suggested a viral etiology. *Id.* at 113.

On September 17, 2012, J.T. saw neurologist Dr. Callahan again for a follow-up after his visits to the emergency room. Ex. 3 at 23-24. J.T. underwent a sleep-deprived EEG, which was abnormal due to “discharges of high voltage spike and wave activity in the left front temporal region.” *Id.* at 24. Dr. Callahan noted that J.T.’s “development ha[d] been normal” and that he had “not had any regression in his development,” and concluded that J.T. had “epilepsy with partial onset seizures with secondary generalization.” *Id.* Dr. Callahan prescribed an escalating dosage of an anticonvulsant (Keppra) and recommended a brain MRI. *Id.* J.T. had the brain MRI on September 26, 2012, and the results were normal. *Id.* at 20-21.

On September 24, 2012, J.T. returned to the emergency room having had two more seizures. Ex. 4 at 120-26. Petitioner Huali Thompson reported that J.T. had stopped taking Keppra because it made him fussy. *Id.* J.T. returned to the emergency room on September 25, 2012, seeming to have “an altered mental status” after the previous day’s seizures. Ex. 7 at 17-28. An MRI the following day was normal. *Id.* at 47-48.

On October 1, 2012, J.T. returned for a follow-up with Dr. Callahan. Ex. 3 at 1-2. Dr. Callahan’s neurological examination revealed no abnormalities. *Id.* Petitioners expressed concern

about the possibility of Dravet syndrome and Dr. Callahan referred J.T. for genetic testing to determine whether he might have an SCN1A genetic variant. *Id.* at 2. J.T. underwent genetic testing and was found to have a small duplication on Xp22.2, but no SCN1A abnormality. *Id.* at 7.

On October 3, 2012, J.T. returned to the emergency room having suffered a seizure that lasted roughly 35 minutes. Ex. 1 at 138. The emergency physician noted that J.T. was alert, but exhibited developmental delays such as decreased tone, inability to sit, and limited control of his hands. *Id.* at 140.

On November 9, 2012, J.T. saw Kwee Thio, MD, at the Pediatric Epilepsy Center at Washington University in St. Louis (“WUSTL”). Ex. 8 at 15-17. Dr. Thio noted that J.T.’s “neurological development is remarkable for having lost some motor milestones since the seizures began.” *Id.* at 16. Dr. Thio opined that “the most likely diagnosis is focal seizures with secondary generalization.” *Id.* Dr. Thio posited that the etiology of J.T.’s condition “may be related to the 144 kb interstitial duplication on [the] short arm of chromosome X (Xp22.2).” *Id.*

On December 28, 2012, J.T. underwent a lumbar puncture, which revealed no evidence of inflammation. Ex. 7 at 237-38.

On February 13, 2013, J.T. saw geneticist Marcia Willing, MD, PhD, at the WUSTL School of Medicine. Ex. 10 at 1-4. Dr. Willing noted the following regarding J.T.’s development:

[J.T.] also has a history of developmental delay, but is making progress. At the time of his first seizure he was 6 months old. He was rolling over and tripod sitting, beginning to position himself on all fours in preparation for crawling, reaching for objects, smiling and cooing. His development was thought to be normal by Dr. Callahan who evaluated him in July at the time of his initial seizures. From reading his Neurology records, it sounds like his development either plateaued or fell off with the onset of seizures; he now seems to be progressing again in his development.

*Id.* at 1. Dr. Willing noted J.T.’s “very small duplication involving the MID1 gene at Xp22.2” and expressed doubt that the duplication explains J.T.’s findings. *Id.* at 3. Dr. Willing recommended further genetic testing. *Id.*

On May 3, 2013, J.T. saw Dr. Thio for a follow-up. Ex. 8 at 3-5. Petitioners reiterated their concerns about his developmental delays. *Id.* at 3. Dr. Thio noted that J.T. was “not able to sit without support and crawl[ed] with his forearms.” *Id.* at 4. Dr. Thio further noted that J.T.’s vocalizations were limited to cooing and babbling and that he was not able to pull himself up to stand. *Id.* at 3. Dr. Thio’s assessment was that J.T. suffered from “focal seizures with secondary generalization, global developmental delay, and hypotonia.” *Id.* at 4. Dr. Thio posited that these issues were related to his gene duplication but could not say definitively. *Id.*

On May 20, 2013, J.T. underwent another lumbar puncture which also revealed no evidence of inflammation. Ex. 7 at 541-42.

In early 2014, after nine months with no seizures, J.T. began having a new kind of seizure in which his eyes rolled back and his head slumped forward. Ex. 7 at 578. These episodes lasted only a few seconds but began to occur 20 to 30 times per day, increasing to 15 to 20 times per hour even with anticonvulsant medication. *Id.* On January 9, 2014, J.T. underwent an EEG which showed clinical and electrographic seizures. Ex. 43 at 28.

On January 28, 2014, J.T. returned to the emergency room for an increase in seizure frequency from 20 per day to 20 per hour, each lasting one to two seconds. Ex. 7 at 568-82. The treating neurologists noted that J.T.’s chromosomal duplication at Xp22.2 included the CDKL5 gene that was “linked to infantile onset epilepsy with global developmental delay and hypotonia,” but felt it was “unclear” whether the chromosomal duplication was the cause of his epileptic syndrome. *Id.*

On January 29, 2014, J.T. underwent an MRI that was normal and yielded no evidence to explain his seizures. Ex. 7 at 604-05.

On February 2, 2014, J.T. again reported to the emergency room for increased seizure frequency, having had roughly 30 seizures so far that morning as opposed to the typical 15 to 20 per day. Ex. 7 at 719-31. A sample of J.T.’s blood was sent for genomic sequencing. *Id.* at 822-31.

At a follow up appointment on June 3, 2014, Dr. Thio noted that, since his appointment on November 15, 2013, J.T. had begun experiencing head drops approximately 20 to 30 times per day. Ex. 43 at 28. He continued to exhibit developmental delays, such as an unstable gait and inability to use words. *Id.*

On June 19, 2014, the results of J.T.’s genomic sequencing revealed a de novo L215V mutation in the GABRA1 gene. Ex. 10 at 26. The authors of the report note that “[m]utations in the GABRA1 gene have been reported in association with juvenile myoclonic epilepsy (JME), childhood absence epilepsy (CAE), idiopathic generalized epilepsy, and Dravet syndrome.” *Id.* (citations omitted). The authors also note that, while the “de novo L215V mutation in the GABRA1 gene has not been reported previously as a disease-causing mutation...[they] interpret L215V as a disease-causing mutation associated with GABRA1-related disorders. Its presence in [J.T.] is associated with the reported developmental delays and epilepsy in [J.T.].” *Id.* at 27.

J.T. saw Dr. Thio again on June 30, 2014, to discuss the results of the genomic sequencing. Ex. 43 at 25. Dr. Thio explained to Petitioners that the L215V mutation combined with the Xp22.2 duplication “may account for [J.T.’s] condition.” *Id.* at 26. Dr. Thio further explained that J.T.’s epilepsy likely has a genetic basis and that “vaccinations probably did not have a causative role in his epilepsy.” *Id.* An EEG that same day revealed that “[i]ndependent interictal discharges in the left and right parasagittal regions [were] consistent with focal or multifocal epilepsies, but also may be seen in generalized epilepsies.” Ex. 42 at 48.

On April 8, 2015, J.T. saw Dr. Thio again because Petitioner Huali Thompson was concerned about his “gait and his mental status.” Ex. 43 at 11. She also reported that J.T. had seizures lasting 1 to 2 seconds daily during which he would sometimes blink his eyes and “appear[]

to fall back slightly,” and at other times his seizures were characterized by “staring and activity arrest.” *Id.* J.T. also experienced more severe seizures about once per week. *Id.* These lasted roughly five minutes and consisted of “activity arrest, apnea, unresponsiveness, and sometimes some jerking of the right side of his mouth.” *Id.*

On April 13, 2015, J.T. saw Orrin Devinsky, MD, at the NYU Epilepsy Clinic. Ex. 20 at 5. Dr. Devinsky noted that J.T.’s seizures began approximately six hours after his DTaP vaccination and that J.T. was “eventually diagnosed with GABRA2 [sic] mutation.” *Id.* His discharge records indicate that he had been diagnosed with Dravet syndrome and “intractable epilepsy” in the past. Ex. 32 at 7.

On May 19, 2015, J.T. returned to NYU to establish a baseline for his enrollment in the Epidiolex (cannabidiol) clinical trial, where he saw Erin Conway, NP. Ex. 20 at 8. Nurse Conway’s impression was of “Dravet Syndrome-GABRA mutation” and intractable epilepsy. *Id.* at 10.

On August 17, 2015, J.T. saw Dr. Devinsky, who noted that J.T. had been seizure-free for nearly 60 days, since June 21, 2015. Ex. 20 at 17-18.

On November 13, 2015, J.T. had a follow-up appointment with Dr. Thio, who noted that J.T.’s condition was “consistent with Dravet syndrome” and that he was enrolled in the cannabidiol trial for Dravet syndrome. Ex. 43 at 8.

On January 4, 2016, Dr. Devinsky wrote a letter stating that “seizures in Dravet Syndrome often occur shortly after vaccinations, as occurred in [J.T.’s] case,” and that “there is extremely strong evidence that [J.T.’s] epilepsy was activated by the third DT/DTaP vaccination on July 7, 2012.” Ex. 24.

On November 21, 2016, J.T. saw Dr. Thio again. Ex. 43 at 2-4. Petitioners reported that, since his previous appointment in May 2016, J.T. had had five to six seizures consisting of “eyes deviating to the right or left with facial cyanosis” and unresponsiveness. *Id.* at 2. His mild seizures lasted roughly five minutes and severe ones lasted up to 30 minutes. *Id.* Dr. Thio noted that, while J.T. continued to have developmental delays, he was “making progress,” and commented that J.T. had spoken more words during the November 21 appointment than Dr. Thio had ever heard him say. *Id.* at 3.

As of July 17, 2020, J.T. was still under the care of Dr. Thio for “epilepsy characterized by focal seizures with bilateral evolution and head drops” and had documented “intellectual disability and hypotonia.” Ex. 139 at 67. Dr. Thio reiterated his opinion that J.T.’s condition is “consistent with Dravet syndrome.” *Id.* at 72. Petitioners declined Dr. Thio’s offer to change J.T.’s antiseizure regime to medications that had recently become available. *Id.*

No additional medical records pertinent to this analysis have been filed.

### **III. Petitioner’s Affidavit and Testimony**

#### **A. Affidavit of John Thompson**

Mr. Thompson filed an affidavit on July 31, 2020. Ex. 136. Mr. Thompson noted that J.T. was the youngest of Petitioners' five children. *Id.* at 1. J.T. was developmentally normal until July 8, 2012. *Id.* at 1-2. Mr. Thompson was away from his family that day as a sitting reserve pilot but had checked in with Ms. Thompson who noted J.T. was fussy after receiving his six-month vaccinations. *Id.* at 2. Later that day, around 9:00pm, J.T. became lifeless, had stopped breathing, and had turned blue. *Id.* Ms. Thompson sought out her neighbors who called 911. *Id.* Mr. Thompson was contacted by his neighbor and immediately drove home upon hearing what had happened. *Id.* J.T. was diagnosed with a febrile seizure and released from the hospital the next day. *Id.*

Mr. Thompson noted that weeks passed and things were normal when J.T. had another seizure. Ex. 136 at 2. J.T. was diagnosed with epilepsy. *Id.* J.T.'s seizures became more frequent and longer over time and he regressed developmentally. *Id.* J.T. then began having "head drop" seizures. *Id.* at 3.

Petitioners noticed that J.T.'s seizures were having a detrimental effect on the family and bought an RV to travel as a family to Alaska. Ex. 136 at 3. Petitioners reached out to medical professionals across the country for several drug studies, and began exchanging emails with Dr. Devinsky at NYU Langone Medical Center. *Id.* Shortly thereafter, J.T. was enrolled in a study with GW Pharmaceuticals, for a drug known as Epidiolex. *Id.* at 3-4. J.T. began to normalize, having a seizure on Father's Day 2015 while in Alaska. *Id.* at 4. He required no medical treatment. *Id.*

The Thompson family returned from their family trip to Alaska where J.T. remained seizure-free until Thanksgiving 2015. Ex. 136 at 4. The five months between Father's Day and Thanksgiving was the longest J.T. had gone without seizures since they first began. *Id.* J.T. continues to be medicated with CBD oil and Depakote. *Id.* J.T. continues to have seizures which are increasing in intensity and frequency again. *Id.*

## **B. Testimony of John Thompson**

Mr. Thompson testified on the first day of the September 23-24, 2020 entitlement hearing. Mr. Thompson is a pilot for FedEx. Tr. at 7. Because of the nature of his job, Ms. Thompson would often take their children to the doctor and have a translator at the appointments, as she is not a native English speaker. *Id.* at 6-7. Mr. Thompson was in Memphis, Tennessee the day that J.T. received his six-month vaccines, as a "sitting reserve" pilot, who are pilots on standby for pilots who get sick or need an additional crew for additional freight. *Id.* at 9. He received a call from his neighbor, Debbie Voss, stating Ms. Thompson had run over to her home with J.T. wearing nothing but her underwear because J.T. was not breathing and was blue. *Id.* at 10. An ambulance had been called and Ms. Voss would update him when she could. *Id.* Mr. Thompson immediately notified crew scheduling and drove approximately three hours directly to the hospital. *Id.* at 11.

Upon arrival to hospital, Mr. Thompson was informed that J.T. had experienced a febrile seizure. Ms. Thompson was in a state of shock. Tr. at 12. The doctors stated that J.T. would be fine as long as he did not have another seizure. *Id.*

J.T. had another seizure approximately two months later on September 11, 2012. Tr. at 13. Mr. Thompson was in Portland for his job but remembered J.T. being hooked up for an EEG by Dr. Callahan, a neurologist, who informed the family that J.T. had abnormal voltage spikes in the front left lobe and diagnosed him with epilepsy. *Id.* at 14. J.T. was no longer developing like Mr. Thompson's other children had and J.T. was "crawling on the floor like a snake because he couldn't hold his head up." *Id.* at 15.

J.T. began seeing Dr. Thio, a neurologist at the Children's Hospital at Washington University in St. Louis. Tr. at 15-16. Dr. Thio diagnosed J.T. with epileptic encephalopathy, which resulted in permanent brain damage. *Id.* Dr. Thio requested Petitioners try to capture on video one of J.T.'s seizures because he was experiencing different types. *Id.* Ms. Thompson began to notice that J.T. looked like he was being electrocuted, which was diagnosed as a head-drop seizure. *Id.* at 16-17. He had more serious seizures where he couldn't breathe and would turn blue, but have less insidious head-drop seizures that were happening much more frequently, up to 700 times per day. *Id.* at 17.

J.T. went through genetic testing that revealed an abnormality in one of his chromosomes, a de novo mutation in the GABRA1 gene. Tr. at 17-18. Petitioners looked at a drug trials and CBD as a possible treatment option. *Id.* at 18-19. Dr. Thio wouldn't entertain CBD because it was still illegal with no proven medical benefit. *Id.* at 19.

Petitioners decided that due to the direness of the situation with J.T., they should go on a family vacation to Alaska. Tr. at 19-20. Right before the trip, Mr. Thompson received a call from the Epilepsy Foundation in St. Louis, recommending he reach out to Dr. Orrin Devinsky. *Id.* at 20. Mr. Thompson sent Dr. Devinsky links he had sent to Dr. Thio of the videos that he and Ms. Thompson had recorded of the seizures J.T. was experiencing. *Id.* at 20-21. Dr. Devinsky requested that they come to the NYU hospital. *Id.* at 21.

J.T. was accepted into the drug study and began to not have seizures. Tr. at 22. J.T. went from being a kid who could not go to school to a child that loved riding the bus to school; "bus" is one of the few words J.T. can speak. *Id.* J.T. is on an individualized education program (IEP) and enjoys music. *Id.* at 23. J.T. knows approximately ten words and can do some simple tasks but is not potty-trained and lacks awareness for his own safety. *Id.* at 23-24. J.T.'s condition has had a dramatic impact on the Thompson family and the other children. *Id.* at 26-28. J.T.'s care in the future is a huge concern for Petitioners given that J.T. will never be able to take care of himself and they are aging and cannot take care of him forever. *Id.* at 29.

#### **IV. Expert Opinions and Qualifications**

##### **A. Petitioners' Expert, Dr. Orrin Devinsky**

###### **1. Qualifications**

Dr. Devinsky received his medical degree from Harvard University and performed a neurology residency at the New York Hospital-Cornell Medical Center Hospital. Ex. 25

(hereinafter “Devinsky CV”) at 1. Dr. Devinsky completed a fellowship at the NIH Clinic Epilepsy Section and Laboratory of Electroencephalography and Clinical Neurophysiology. *Id.* Dr. Devinsky is board certified in neurology and clinical neurophysiology. *Id.* Dr. Devinsky is a professor of psychiatry and neurosurgery at the NYU School of Medicine and Director of the NYU Comprehensive Epilepsy Center and Saint Barnabas Institute of Neurology & Neurosurgery. *Id.* Dr. Devinsky has performed extensive research on epilepsy and SUDEP (sudden unexpected death in epilepsy) as a principal investigator. *See id.* at 5-8. Dr. Devinsky has published 345 peer-reviewed articles and 83 books related to epilepsy. *Id.* at 8-33, 34-38.

## **2. Letter**

Dr. Devinsky submitted a letter in this case written on January 4, 2016. Ex. 24. In this letter, Dr. Devinsky confirmed that J.T. was being seen for treatment resistant epilepsy and severe pervasive developmental delays. *Id.* Dr. Devinsky became involved with J.T.’s medical care when he was enrolled in an investigative drug trial for Dravet syndrome. *Id.* Dr. Devinsky noted that seizures in Dravet syndrome often occur shortly after vaccinations, as with J.T., and that “there is extremely strong evidence that [J.T.’s] epilepsy was activated by the third DT/DTaP vaccination on July 7, 2012.” *Id.*

## **B. Petitioner’s Expert, Dr. Yuval Shafrir**

Dr. Shafrir provided four expert reports in this case and testified at the entitlement hearing. Exs. 45 (hereinafter “First Shafrir Rep.”); 101 (hereinafter “Second Shafrir Rep.”); 114 (hereinafter “Third Shafrir Rep.”); 146 (hereinafter “Fourth Shafrir Rep.”).

### **1. Qualifications**

Dr. Yuval Shafrir is a pediatric neurologist at Sinai Hospital in Baltimore, Maryland. Shafrir CV at 3. He attended Tel Aviv University Sackler School of Medicine in Israel from 1976 to 1982 and conducted his pediatric residency rotations in Israel. *Id.* at 1. After moving to the United States, he completed a pediatric residency at Cornell University Medical College. *Id.* Dr. Shafrir then completed a fellowship in pediatric neurology at Washington University Medical Center in St. Louis and a second fellowship in pediatric neurophysiology and epileptology at Miami Children’s Hospital. *Id.* Dr. Shafrir is board-certified in neurology with a specialty in pediatric neurology, clinical neurophysiology, and epilepsy. *Id.* at 2. In addition to his active private practice in pediatric neurology, Dr. Shafrir also served as an Assistant Professor in Neurology and Pediatrics at multiple academic and medical institutions, including United Services University of the Health Sciences, Georgetown University School of Medicine, the University of Oklahoma School of Medicine, and most recently, the University of Maryland School of Medicine. *Id.* at 2-3. He has conducted numerous clinical studies in pediatric neurology and has published more than 20 peer-reviewed articles and abstracts. *Id.* at 3-6. Dr. Shafrir has treated five patients with Dravet syndrome and 20 patients with early onset epileptic encephalopathy. Tr. at 39. I recognized Dr. Shafrir as an expert in pediatric neurology and epileptology. *Id.* at 46.

### **2. First Expert Report**

In his first expert report, Dr. Shafrir began his discussion by opining that J.T. “does not have typical Dravet syndrome.” First Shafrir Rep. at 50. He noted that J.T.’s medical history did not include three major characteristics of Dravet syndrome: (1) a normal EEG after initial seizures (J.T.’s EEG was abnormal from the beginning); (2) prolonged hemi-convulsion; and (3) a period of one to two years of seizures before the onset of delay (J.T.’s delay appeared immediately after seizure onset). *Id.* at 50-51. Dr. Shafrir noted that pediatric epileptic encephalopathies may resemble Dravet syndrome, but opined that the use of the term in J.T.’s case was likely applied in order to qualify J.T. for the cannabidiol clinical trial at NYU. *Id.* at 51.

Dr. Shafrir also argued that “[i]t is unlikely that the GABRA1 mutation is the sole cause of [J.T.’s] catastrophic epileptic encephalopathy.” First Shafrir Rep. at 51. Dr. Shafrir noted that J.T.’s specific mutation has never been reported before, and that the report of his whole exome sequencing indicated that the L215V mutation “is not likely to impact secondary protein structure as these residues share similar properties.” *Id.* at 51-52. He opined that, while there is support in the medical literature for a link between certain GABRA1 mutations and epilepsy syndromes, the L215V is a conservative mutation that would not be expected to cause J.T.’s condition. *Id.* at 52.

Dr. Shafrir expressed the opinion that J.T. “probably has some abnormalities in his immune system.” First Shafrir Rep. at 53. He noted that J.T. has been seen for various infections over the course of his life and that he “is definitely having many more infections than a normal child.” *Id.* Dr. Shafrir suggested that an IgA deficiency “could explain a lot of his symptoms.” *Id.*

Dr. Shafrir asserted that J.T. “has epileptic encephalopathy with an onset occurring in less than 24 hours after his six-month immunization.” First Shafrir Rep. at 53. Dr. Shafrir argued that J.T.’s initial seizure was the initial presentation of epileptic encephalopathy and that, in the absence of a gene mutation to explain it, vaccination is the only explanation left. *Id.*

Dr. Shafrir next examined each of the *Althen* prongs in turn. His theory of causation is that, “[b]ecause of [a] yet unidentified genetic susceptibility,” J.T. had an abnormal reaction to the vaccines, which in turn caused his immune system to attack his brain. First Shafrir Rep. at 55. Dr. Shafrir cited Tishler and Schoenfeld for the proposition that a genetic predisposition for autoimmunity can raise the risk of autoimmune disease brought on by vaccines. *Id.* Dr. Shafrir proposed that the autoimmune attack may have impacted ion channels in J.T.’s brain that control neuronal excitability. *Id.* Dr. Shafrir posited that J.T.’s autoimmune response persisted because of epitope spreading and bystander activation, and that he developed epilepsy due to changes in his brain brought about by ongoing seizures. *Id.* According to Dr. Shafrir, it was these neural changes that worsened his seizures and delayed his psychomotor development. *Id.* at 56.

In support of his theory of causation, Dr. Shafrir cited to several articles from the medical literature. First, he noted that the DTaP vaccine has been known to cause autoimmune phenomena such as acute disseminated encephalomyelitis, autoimmune hemolytic anemia, and autoimmune neuropathies. First Shafrir Rep. at 56. Second, Dr. Shafrir cited to a study showing that the H1N1 influenza vaccination had been shown to cause narcolepsy in several children in Europe, and that narcolepsy is strongly associated with genetic susceptibility. *Id.* Third, Dr. Shafrir noted that the pertussis vaccine has been shown to cause inflammation in the brains of laboratory animals. *Id.* at 57. Fourth, Dr. Shafrir cited a study that showed that EEGs of children with a history of seizures

showed epileptic discharges after DTaP vaccination. *Id.* Fifth, Dr. Shafrir cited to multiple studies suggesting a link between vaccines and autoimmune encephalitis. *Id.* at 57-58. Sixth, Dr. Shafrir cited a study showing significant homology between components of the DTaP vaccine and proteins in the brain. *Id.* at 58-59. This, he argues, is evidence that molecular mimicry could be the basis for autoimmune attacks on the brain following vaccination, particularly in individuals with genetic susceptibility. *Id.* at 59. Finally, he cited to multiple articles to support his contention that a single seizure can cause long-term effects in the brain, including receptors and messengers and gene expression, as well as increasing the likelihood of future seizures. *Id.* at 59-60.

In his analysis of *Althen* prong two, Dr. Shafrir assumed that J.T. possessed a deficit in immune regulation prior to receiving the vaccines. First Shafrir Rep. at 60. He posited that, “either through pre-existing autoantibodies, or throwing rapid induction of autoantibodies by immune memory cells, or activation of components of the innate immune system,” J.T. suffered brain injury, seizures, and changes in gene expression in his brain. *Id.* Dr. Shafrir argued that the persistence of J.T.’s epileptic encephalopathy years after vaccination could be explained by epitope spread, in which the immune system continues to attack self-antigens that are similar to the vaccine antigens. *Id.* at 61.

Addressing *Althen* prong three, Dr. Shafrir stated that the temporal link “is obvious from the medical records.” First Shafrir Rep. at 62.

### 3. Second Expert Report

In his second expert report, Dr. Shafrir responded to Dr. Kohrman’s critiques. Second Shafrir Rep. at 1. First, Dr. Shafrir refuted Dr. Kohrman’s argument that J.T.’s medical history does not contain evidence of brain inflammation by pointing out that even patients with more severe autoimmune encephalopathies than J.T. often do not exhibit inflammation. *Id.*

Dr. Shafrir rebutted Dr. Kohrman’s assessment that J.T.’s genetic mutation caused his condition. Second Shafrir Rep. at 2. Dr. Shafrir opined that Dr. Kohrman had misinterpreted J.T.’s genetic sequencing reports and argued that J.T.’s mutation would not be likely to cause changes to the protein structure or function. *Id.* Dr. Shafrir pointed out that other patients with the same mutation have mild epileptic encephalopathy. *Id.* at 2-3.

Dr. Shafrir also responded to Dr. Kohrman’s citation to McIntosh, et al., in which the authors allude to some patients with the SCN1A mutation being “destined” to develop Dravet syndrome, even if vaccination may sometimes accelerate onset. Second Shafrir Rep. at 3. Dr. Shafrir noted his opposition to the idea of being “destined” to develop Dravet Syndrome and pointed out later studies that showed (1) that the age of onset of seizures makes a significant difference in outcomes, and (2) that some patients with the mutation remain asymptomatic. *Id.* Dr. Shafrir added that, even if the genetic mutation is the cause of J.T.’s epileptic encephalopathy, the early onset of seizures (and thus his poor prognosis) was triggered by his vaccination. *Id.* at 4. Dr. Shafrir opined that the genetic mutation is more likely to be a risk factor for J.T.’s condition rather than its sole cause. *Id.* Finally, Dr. Shafrir stated that even if the vaccine was not the sole cause of J.T.’s condition, it at least significantly aggravated his preexisting genetic susceptibility. *Id.* at 5.

#### 4. Third Expert Report

In his third expert report, Dr. Shafrir responded to the opinion of Dr. Raymond. Third Shafrir Rep. at 1. Dr. Shafrir summarized Respondent's theory of causation as being that J.T.'s "severe and disabling epileptic encephalopathy was triggered by the fever and would have occurred anyway because of his genetic mutation." *Id.* Dr. Shafrir reiterated his opinion that Dravet syndrome is not the correct diagnosis of J.T.'s condition, but he cited medical literature supporting the strong association between Dravet syndrome and immunization. *Id.* at 2.

Dr. Shafrir noted that mutations on the GABRA1 gene have been linked to generalized epilepsies and febrile seizures but opined that J.T.'s condition is so much more severe than cases discussed in the literature that the mutation is unlikely to be the sole cause. Third Shafrir Rep. at 2-3. Dr. Shafrir also opined that, while little is known about the L215V mutation that J.T. has, it does not meet any of the criteria for pathogenic mutations set forth by ClinVar. *Id.* at 4. Dr. Shafrir went on to argue that the L215V mutation is not enough on its own to explain the seriousness of J.T.'s condition. *Id.* at 5. Most patients who have reported this mutation on ClinVar exhibit less serious conditions such as juvenile myoclonic epilepsy and absence epilepsy without cognitive impairment or developmental delays. *Id.*

Dr. Shafrir went on to reiterate his disagreement with the authors of McIntosh, et al., who stated that some patients with the SCN1A mutation are "destined" to develop Dravet syndrome. Third Shafrir Rep. at 6. He noted that most genetic variants lack enough data to be certain about whether they will or will not cause disease, and that the language in the McIntosh, et al., article goes too far. *Id.* at 6-7. Dr. Shafrir opined that "[i]t may very well be that the GABRA1 mutation that [J.T.] carries disrupts his immunoregulatory system and causes abnormal enhancement of his immune reaction." *Id.* at 9. Such an abnormal reaction, Dr. Shafrir argued, may have been triggered by the vaccine and caused J.T.'s condition. *Id.*

Dr. Shafrir concluded by opining that there is little doubt that the vaccine triggered J.T.'s severe epileptic encephalopathy and extreme disability. Third Shafrir Rep. at 14. He added that there is no proof that J.T.'s condition would have developed had the vaccine not triggered it. *Id.*

#### 5. Fourth Expert Report

In his fourth expert report, Dr. Shafrir responded to discrete points raised by Drs. MacGinnitie and Raymond and provided a summary of his opinions in this case. Fourth Shafrir Rep.

In response to Dr. MacGinnitie's opinion that vaccination does not cause a notable inflammatory response, Dr. Shafrir opined that normally is true, but that J.T. likely had an abnormal reaction due to a preexisting genetic susceptibility. Fourth Shafrir Rep. at 16. Dr. Shafrir further noted that Dr. MacGinnitie's opinion that the DTaP vaccine is associated with seizure and epilepsy in patients with Dravet syndrome is not inconsistent with Dr. Shafrir's opinion that J.T.'s DTaP vaccination contributed to his extreme encephalopathy. *Id.*

Dr. Shafrir agreed with Dr. Raymond's opinion that the GABRA1 mutation that J.T. carries is pathogenic. Fourth Shafrir Rep. at 19. However, he argued that the literature supports this contention that the mutation typically causes much milder forms of epileptic encephalopathy than J.T. exhibits. *Id.* He noted that "the severity of a genetic epilepsy can be modified by environmental factors such as early seizures," and reiterated his opinion that J.T.'s condition was triggered by the vaccine. *Id.* at 19-20.

In closing, Dr. Shafrir summarized his opinions in the case as follows: First, J.T.'s epileptic encephalopathy was triggered by the vaccines he received on July 7, 2012. Fourth Shafrir Rep. at 20. Second, J.T.'s GABRA1 mutation is not sufficient to explain the severity of his condition. *Id.* at 20-21. Third, although J.T. does not carry an SCN1A mutation, the literature on this mutation is instructive in that it shows a wide variety in presentation among epileptic encephalopathy patients. *Id.* at 21. Fourth, a genetic mutation does not guarantee that a patient will eventually develop Dravet syndrome, as the authors of McIntosh, et al., suggest. *Id.* at 21-23. Fifth, there is very little data about the relationship between GABRA1 mutation and vaccination. *Id.* at 23. Sixth, studies involving laboratory animals have shown that early seizures have a profound effect on development of epilepsy. *Id.* Seventh, J.T.'s genetic mutation affects his immune system and may have caused an excessive immune response in reaction to the vaccines. *Id.* Eighth, "[a]nti-neuronal antibodies are not rare in infants and toddlers with complex febrile seizures and new onset epilepsies." *Id.* These may be evidence of related immune phenomena such as might cause conditions like J.T.'s. *Id.* Finally, J.T.'s genetic mutation is at least "likely pathogenic," but is not likely to be the sole cause of J.T.'s condition. *Id.*

## 6. Testimony

During the entitlement hearing, Dr. Shafrir opined that J.T.'s genetic mutation is pathogenic. Tr. at 47. Dr. Shafrir opined that but for J.T.'s six-month vaccinations, he would have experienced idiopathic generalized epilepsy but the vaccines triggered early infant epileptic encephalopathy. *Id.* at 48-49. Idiopathic generalized epilepsy causes seizures, but patients can live a normal life. *Id.* at 49. Early infant epileptic encephalopathy is a severely debilitating condition that leads to decline in cognition and severe disability. *Id.* Dr. Shafrir's clinical diagnosis for J.T. with the knowledge that he has a GABRA1 mutation is that he has early infantile epileptic encephalopathy 19 or EIEE19. *Id.* at 50. Dr. Shafrir reiterated his opinion that J.T.'s clinical picture is not consistent with typical Dravet syndrome. *Id.* However, he also testified that, should I find that Dravet syndrome is the most likely diagnosis, that this would not change his opinion in this case. *Id.* at 58. He opined that the studies linking Dravet syndrome to SCN1A mutation are not applicable here because J.T.'s GABRA1 mutation and the SCN1A mutation represent "completely different neurological systems and different neurological segments." *Id.* at 59.

Dr. Shafrir disagreed with Respondent's experts' opinion that J.T. did not experience a regression. Tr. at 56. He noted that J.T.'s parents raised the issue of a regression with Dr. Thio on August 31, 2012, and that "Dr. Thio confirmed the presence of a regression." *Id.* at 56-57. He noted that it was especially compelling that J.T. was not finger-feeding himself at the age of eight months, noting that this was "clearly abnormal." *Id.* at 197. Dr. Shafrir acknowledged that the medical record does not contain evidence that J.T. had ever begun feeding himself, but pointed out that this skill is not part of the Denver Motor Evaluation used to assess developmental progress

and so likely would not have appeared in the medical record. *Id.* at 246. Dr. Shafrir opined that children finger-feed themselves at the age of six months, and thus J.T.’s inability to do so at the age of eight months constitutes a delay. *Id.* at 247. Dr. Shafrir also testified that a regression would not be visible on MRI. *Id.* at 255.

Dr. Shafrir opined that the aluminum adjuvant in the Pentacel vaccine caused an abnormally strong immunological reaction in J.T. due to his underlying genetic mutation. Tr. at 60-62. He added that the GABRA1 receptor, the locus of J.T.’s genetic mutation, “plays a major role in the regulation of the immune system.” *Id.* at 62. The mutation makes J.T. more susceptible to an exaggerated immune response. *Id.* at 63. Dr. Shafrir went on to opine that the exaggerated immune reaction to the Pentacel vaccine caused the release of pro-inflammatory cytokines which crossed the blood-brain barrier and caused his first seizure hours after vaccination. *Id.* at 64. He opined that the fever and irritability that J.T. exhibited shortly after vaccination may be evidence of cytokine activity in his brain. *Id.* at 68. He testified that this timing is consistent with his theory that the vaccine overactivated J.T.’s immune system. *Id.* at 90.

Dr. Shafrir opined that J.T.’s continued deterioration may be the result of antibodies. Tr. at 69. He explained that, while cytokines normally recede within days after vaccinations, the production of antibodies that attack neuronal channels in J.T.’s brain might explain why his condition continued to develop long after receiving the Pentacel vaccine. *Id.* at 72. On cross-examination, Dr. Shafrir acknowledged that there is medical literature concluding that the presence of antibodies “is unlikely to be a causal explanation for epilepsy.” *Id.* at 129.

Dr. Shafrir also opined that the initial seizure alone could have damaged J.T.’s brain. He testified, “it could very well be that the initial seizure already sealed his fate.” Tr. at 72. Dr. Shafrir testified that his main theory is that “the onset of [J.T.’s] EIEE19 was triggered by vaccination. This can be explained by different mechanisms. The most likely one is activation through cytokines.” *Id.* at 151. He further testified that the perpetuation of J.T.’s condition “can be caused by the fact that there was onset of the cascade of events that led to [an] irreversible situation in the brain and persistence of epileptic encephalopathy that otherwise would not have occurred.” *Id.*

Dr. Shafrir noted that there is no medical literature exploring a relationship between vaccines and GABRA1-related epileptic encephalopathy. Tr. at 84.

Dr. Shafrir opined that animal studies in the medical literature “have demonstrated that the deleterious consequences of seizures strongly depend on the developmental stage at which they occur.” Tr. at 99. The earlier seizures begin, the worse the prognosis. *Id.* at 102-03. Dr. Shafrir opined that the Pentacel vaccination caused J.T. to develop early onset EIEE19 by overactivating his immune system and causing seizures. *Id.* at 104. He concluded by opining that, but for the vaccinations he received, J.T. would have developed idiopathic generalized epilepsy, a much milder condition than EIEE19. *Id.* at 108.

### **C. Respondent’s Expert, Dr. Michael Kohrman**

#### **1. Qualifications**

Dr. Kohrman's CV was filed as Exhibit B (hereinafter "Kohrman CV"). Dr. Kohrman received his medical degree from Rush Medical College and performed his pediatrics residency at The University of Chicago Hospitals and Clinics. Kohrman CV at 2. Dr. Kohrman did a fellowship in pediatric neurology at the University of Chicago Hospitals and an electroencephalography fellowship at the University of Illinois, Chicago. *Id.* at 2. Dr. Kohrman is currently Director of Pediatric Neurology at Akron Children's Hospital and was the Director of Pediatric Epilepsy Fellowship Program. *Id.* at 1. Dr. Kohrman is board certified in neurology (with a subspecialty certification in child neurology, epilepsy, and clinical neurophysiology), pediatrics, and sleep medicine. *Id.* at 2. Dr. Kohrman has published 59 peer-reviewed papers and 14 book chapters. *Id.* at 2-8, 8-9.

Dr. Kohrman filed three expert reports. Exs. A (hereinafter "First Kohrman Rep."); C (hereinafter "Second Kohrman Rep."); and L (hereinafter "Third Kohrman Rep."). Dr. Kohrman did not testify at the entitlement hearing.

## 2. First Expert Report

In his first expert report, Dr. Kohrman opined that J.T. has Dravet syndrome secondary to a mutation on the GABRA1 gene. First Kohrman Rep. at 9. He noted that "[h]yperthermia triggers seizures in most patients with Dravet syndrome." *Id.*

Dr. Kohrman noted that J.T.'s GABRA1 mutation is located at L215V and cited medical literature finding that Dravet syndrome is associated with genetic mutation at R214H, only one amino acid away from J.T.'s mutation. First Kohrman Rep. at 10. Dr. Kohrman also noted that the mutation at R214H "produces a functional change in the receptor response to GABA, the major inhibitory neurotransmitter in the nervous system...responsible for stopping seizures." *Id.*

Dr. Kohrman opined "[t]here is strong evidence that vaccination causing fever can trigger the first seizure in Dravet syndrome," but "there is no evidence that vaccination alters the course in Dravet syndrome." First Kohrman Rep. at 13. Dr. Kohrman cited McIntosh, et al., who studied children with Dravet syndrome caused by SCN1A mutations whose seizure onset was either vaccination-proximate or vaccination-distant. *Id.* McIntosh, et al., found "no differences in intellectual outcome, subsequent seizure type, or mutation type between the two groups." *Id.* (citation omitted). The authors "found no evidence that vaccinations before or after disease onset affect outcome." *Id.* (citation omitted).

Dr. Kohrman also opined that J.T.'s medical record contains no evidence of autoimmune process (i.e., J.T.'s lumbar punctures on December 28, 2012, and May 20, 2014, and his MRI in January 2014 were all normal). First Kohrman Rep. at 15. He argued that there is no evidence that J.T.'s Dravet syndrome was caused by the vaccine or that the vaccine altered the course of his condition. *Id.*

## 3. Second Expert Report

In his second expert report, Dr. Kohrman responded to Dr. Shafrir's expert report. Second Kohrman Rep. at 1. Dr. Kohrman disagreed with Dr. Shafrir's opinion that the etiology of J.T.'s

seizure disorder is autoimmune encephalopathy, arguing instead that the medical record contains “clear evidence of a pathologic mutation known to cause Dravet syndrome.” *Id.* Dr. Kohrman also argued that J.T.’s condition does not meet the criteria for autoimmune encephalopathy as defined by Hacohen, et al. *Id.* Dr. Kohrman argued that Dravet syndrome is the correct diagnosis for J.T. because his treating physician, Dr. Thio, concluded as much, and Dr. Devinsky admitted him to the cannabidiol trial for Dravet patients. *Id.* at 2.

Dr. Kohrman also argued that J.T.’s GABRA1 mutation is pathological and criticized Dr. Shafrir’s reliance on medical literature dealing with the SCN1A mutation, which J.T. does not have. Second Kohrman Rep. at 3-4.

#### **4. Third Expert Report**

In his third expert report, Dr. Kohrman responded to Dr. Raymond’s expert opinion. Third Kohrman Rep. at 1. Dr. Kohrman agreed with Dr. Raymond’s conclusion that the GABRA1 mutation is a cause of J.T.’s early infantile epileptic encephalopathy and the clinical diagnosis of Dravet syndrome. *Id.* He also agreed with Dr. Raymond’s conclusion that there is no evidence of an autoimmune cause for J.T.’s condition. *Id.*

### **D. Respondent’s Expert, Dr. Gerald Raymond**

#### **1. Qualifications**

Dr. Raymond’s CV was filed as Exhibit E (hereinafter “Raymond CV”). Dr. Gerald Raymond is a pediatric neurologist who specializes in neuropathology and genetics. Raymond CV at 1. He attended the University of Connecticut School of Medicine from 1980-1984. *Id.* After completing medical school, Dr. Raymond performed residency rotations in pediatrics and neurology at the Johns Hopkins Hospital and the Massachusetts General Hospital. *Id.* He then performed a fellowship in developmental neuropathology at Université Catholique de Louvain in Brussels, Belgium, and an additional fellowship in genetics and teratology at Harvard Medical School. *Id.* Dr. Raymond is board-certified in pediatrics, clinical genetics, and neurology, with special competency in child neurology. *Id.* Dr. Raymond is a Professor in Neurology at the Johns Hopkins School of Medicine and was the Director off Neurogenetic Research at the Kennedy Krieger Institute/Johns Hopkins Hospital from 2007-2012. *Id.* at 2. Dr. Raymond has published 117 peer-reviewed papers and 17 book chapters. *Id.* at 3-10, 14-15. I recognized Dr. Raymond as an expert in pediatric neurology and genetics. Tr. at 298-99.

Dr. Raymond filed two expert reports in this case. Exs. D (hereinafter “First Raymond Rep.”); J (hereinafter “Second Raymond Rep.”).

#### **2. First Expert Report**

In his first expert report, Dr. Raymond opined that J.T. suffers from epileptic encephalopathy arising from a GABRA1 mutation, and that his condition was not caused or exacerbated by the vaccines he received. First Raymond Rep. at 15.

Dr. Raymond noted that Drs. Devinsky and Thio diagnosed J.T. with Dravet syndrome and Dr. Raymond did not disagree with that diagnosis. *See, generally,* First Raymond Rep. Dr. Raymond acknowledged that the majority of patients with Dravet syndrome carry SCN1A mutations, but noted that Dravet syndrome is, for the time being, a clinical diagnosis and is not restricted to patients with SCN1A mutations. *Id.* at 5.

Dr. Raymond cited to studies linking GABRA1 mutation with Dravet syndrome and severe developmental delays. First Raymond Rep. at 6. Dr. Raymond noted that the diagnostic criteria for Dravet syndrome as compared with other epileptic encephalopathies are somewhat blurred, and so it is difficult to state with certainty whether a patient with a GABRA1 mutation has the Dravet syndrome phenotype. *Id.*

Dr. Raymond explained the evidence suggesting that the GABRA1 mutation J.T. carries caused his epileptic encephalopathy. First Raymond Rep. at 6-7. First, J.T.'s mutation arose de novo and was not inherited, which is "a powerful indicator that it is disease causing." *Id.* at 7. Second, J.T.'s mutation "has occurred in an area that is a functionally critical domain and a region that has been associated with other deleterious mutations." *Id.* Dr. Raymond acknowledged that "only a limited subset of variants in GABRA1 have been described in sufficient detail to understand the full spectrum of disease of mutations in this region." *Id.*

Dr. Raymond criticized Dr. Devinsky's conclusion that there is "extremely strong evidence" that the DTaP vaccine caused J.T.'s condition. First Raymond Rep. at 7. Dr. Raymond opined that Dr. Devinsky provided no support for this conclusion and no mechanism by which the vaccine supposedly triggered J.T.'s epilepsy. *Id.*

Dr. Raymond discussed the paper by McIntosh, et al., in which the authors found that "vaccination was wrongly blamed as an acquired cause of a genetic disorder and the hypothesis that vaccination was the causal factor in their cohort could be rejected." First Raymond Rep. at 7. Dr. Raymond explained that McIntosh, et al., examined children with Dravet syndrome who experienced seizure onset the day of or day after vaccination (vaccine-proximate) and children with Dravet syndrome who experienced seizure onset later than that (vaccine-distant). *Id.* Dr. Raymond noted that McIntosh, et al., found that seizure onset tended to be at a younger age among the vaccine-proximate group, but that "all other clinical outcome measures" were the same for both groups. *Id.* Accordingly, the authors concluded that "vaccination was not playing a role in the etiology of Dravet syndrome." *Id.*

Dr. Raymond disagreed with Dr. Shafrir's argument that J.T.'s genetic mutation is a conservative one involving similar amino acids, and thus would not likely cause a serious disorder. First Raymond Rep. at 10. Dr. Raymond pointed out that "there are many examples in genetics of significant and severe disorders resulting from mutations that change the amino acid from leucine to valine." *Id.* Dr. Raymond explained that "the reason that conservative amino acid substitutions can in some instances be tolerated and in others be devastating has to do with the location of the change and how it ultimately affects the structure and function of the protein." *Id.* Dr. Raymond pointed out that leucine to valine substitutions affect the helix structure of many proteins, which can impact their function. *Id.*

Dr. Raymond opined that, based on the medical literature, it is likely that the age at the time of seizure onset is a better predictor of the severity of the disorder a patient will develop than variations in DNA. First Raymond Rep. at 11. He noted that seizure onset at a younger age correlates with more serious disorders. *Id.*

Dr. Raymond also disagreed with Dr. Shafrir's assertion that J.T. suffers from an autoimmune encephalitis. First Raymond Rep. at 13. He noted that J.T. does not meet the diagnostic criteria for this condition proposed by Ho, et al. *Id.* He further opined that "there is no evidence here that [J.T.] has an autoimmune disease affecting his brain." *Id.*

### 3. Second Expert Report

In his second expert report, Dr. Raymond responded to several of Dr. Shafrir's points. Second Raymond Rep.

First, Dr. Raymond reiterated his opinion that J.T. has Dravet syndrome. Second Raymond Rep. at 1. He disagreed with Dr. Shafrir's opinion that J.T.'s medical record shows regression after his seizures began. *Id.* at 2. Dr. Raymond pointed out that there is no evidence of loss of skills and that J.T.'s pediatrician stated that J.T. was still meeting developmental expectations on August 31, 2012, over a month after vaccination. *Id.*

Dr. Raymond also disagreed with Dr. Shafrir's opinion that J.T.'s mutation is not pathogenic. Second Raymond Rep. at 3. Dr. Raymond reiterated that the fact J.T.'s variant arose *de novo* is strong evidence of its pathogenicity. *Id.* at 4. Dr. Raymond also noted that the designation "likely pathogenic" in ClinVar means that there is greater than 90% certainty that the variant is disease-causing. *Id.* at 6-7.

Dr. Raymond also disagreed with Dr. Shafrir's observation that there is no significance to the lack of benign variants in and around the location of J.T.'s variant. Second Raymond Rep. at 7. Dr. Raymond opined that there is significance to the lack of benign variants because, "if mutations do not result in change in the functional protein, they persist and accumulate in the population. As we have seen, the mutation found in [J.T.] has never been identified before." *Id.*

Dr. Raymond next criticized Dr. Shafrir's interpretation of the statement in the McIntosh, et al., article regarding "destiny" in relation to genetic variants. Second Raymond Rep. at 8. Dr. Raymond opined that Dr. Shafrir takes this statement out of context, and that McIntosh, et al., were not arguing that patients with a particular genetic mutation are "destined" to develop Dravet syndrome. *Id.*

Dr. Raymond reiterated his opinion that "there is no evidence that [J.T.] has ... disruption in his immune system or an increase in inflammatory state." Second Raymond Rep. at 10. He cited medical literature supporting the view that the age at which a patient experiences seizure onset does not change the ultimate nature of the patient's condition, but that it "can help temper discussions about prognosis." *Id.* at 11.

### 4. Testimony

Dr. Raymond first provided a description of Dravet syndrome. Tr. at 300. He testified it is a clinical syndrome in children who have severe myoclonic epilepsy in infancy and have normal development up to six to twelve months of age. *Id.* Dravet syndrome has been closely linked to the SCN1A gene but remains a clinical diagnosis. *Id.* at 300-01. There are a number of genes that have been linked to Dravet syndrome: SCN1A, GABRA, SCN1B, and PDCH19. *Id.* at 301-02.

Dr. Raymond testified that after the July febrile seizure, J.T. returned to baseline and it was only in September-November 2012 that J.T. began to developmentally plateau. Tr. at 307. The medications that J.T. was prescribed likely had effects on his personality and responsiveness. *Id.*

Dr. Raymond discussed exhibit K13, which he described as documenting a simpler variant than J.T.'s except with an amino acid substitution from leucine to isoleucine (as opposed to valine in J.T.'s case). Tr. at 318. Dr. Raymond testified that "any change here from leucine to anything else, including the two other similar amino acids, valine and isoleucine, is not tolerated, and this individual is designated as having EIEE19." *Id.* at 319.

ClinVar is a curated database of known genetic mutations and disorders. Tr. at 326. Dr. Raymond testified exhibit 117 shows that position 214 (next to 215, J.T.'s mutation) on the GABRA1 gene is also associated with EIEE19. *Id.* at 332.

Dr. Raymond testified that the medical literature concludes there are a spectrum of phenotypes associated with the GABRA1 mutation. Tr. at 340. For example, Johannesen et al. noted that "the phenotypic spectrum varied from unspecified epilepsies to juvenile myoclonic epilepsies to one family with an idiopathic generalized epilepsy, one family with generalized epilepsy with febrile seizures plus, and then 11 individuals with severe epileptic encephalopathies." Tr. at 341; citing Johannesen et al., *Phenotypic Spectrum of GABRA1 From generalized epilepsies to severe epileptic encephalopathies*, NEUROLOGY 87, 1140-51 (2016) (filed as Ex. F10). Dr. Raymond noted that the majority had severe phenotypes. Tr. at 341.

Dr. Raymond also discussed medical literature cited by Dr. Shafrir. Tr. at 345-49. In discussing the Wei paper (Ex. 57), Dr. Raymond opined that Wei likely mischaracterized the L215V variant as being associated with idiopathic generalized epilepsy, a much milder form of epilepsy than EIEE19. *Id.* at 344.

Dr. Raymond testified that the McIntosh paper and others found that children with a SCN1A gene mutation who experienced a vaccine proximate seizure may have earlier onset of seizures, but not a worse outcome than children who did not experience a vaccine proximate seizure. Tr. at 350. However, Dr. Raymond testified that it was not appropriate to extrapolate the findings from SCN1A studies to GABRA1. *Id.* at 387.

Regarding J.T.'s presentation, the testimony from Mr. Thompson did not change his views. Tr. at 354. J.T. was seemingly normal one month after vaccination (August 31<sup>st</sup>), and then there was an increase in his seizure activity and then a plateauing, not a true regression. *Id.* at 355. J.T.'s appointment with Dr. Thio on November 9, 2012 was the first mention of concern over losing developmental milestones. *Id.* at 355-56; see also Ex. 8 at 16. Mr. Thompson informed Dr. Thio

that he could no longer sit independently and was no longer crawling; this is however not what Dr. Thio observed at the appointment, J.T. was able to stand and bear weight on his legs, sat without support, and his neurological exam was normal with mild axial and appendicular hypotonia. Tr. at 356. Dr. Raymond testified that this constituted plateauing, not regression. *Id.*

Dr. Raymond testified that the GABRA1 mutation, specifically the L215V leucine to valine mutation, is the sole cause of J.T.'s EIEE19. Tr. at 362. Variations in the GABRA1 gene cause the variance in severity. *Id.* at 365. As another example, the R214 histidine and R214 cysteine mutations are associated with severe phenotypes. *Id.* It is unclear to Dr. Raymond whether J.T.'s febrile seizure on July 7, 2012 is related to his epileptic encephalopathy. *Id.* at 367.

Finally, Dr. Raymond testified that J.T.'s initial seizure on July 7, 2012, if caused by the DTaP vaccine he received the same day, would not affect his opinion. Nor would J.T. experiencing some possible regression close in time to the receipt of the vaccine. Tr. at 389.

#### **E. Respondent's Expert, Dr. Andrew MacGinnitie**

##### **1. Qualifications**

Dr. MacGinnitie's CV is filed as Ex. H (hereinafter "MacGinnitie CV"). Dr. MacGinnitie received a PhD in pathology and medical degree from the University of Chicago Pritzker School of Medicine. MacGinnitie CV at 1. Dr. MacGinnitie completed a pediatrics residency at the Boston Combined Residency Program, an allergy/immunology fellowship at the Children's Hospital of Boston, and a pediatrics clinical fellowship at Harvard Medical School. *Id.* Dr. MacGinnitie is currently an associate professor of pediatrics at Harvard Medical School. *Id.* at 2. I recognized Dr. MacGinnitie as an expert in pediatric immunology. Tr. at 267.

##### **2. Expert Report**

Dr. MacGinnitie filed one expert report in this case. Ex. G (hereinafter "MacGinnitie Rep."). Dr. MacGinnitie stated that J.T. has filed no evidence that he suffered an autoimmune reaction. MacGinnitie Rep. at 5. J.T. had a lumbar puncture and CSF analysis performed on December 28, 2012 and May 20, 2013, which showed no evidence of inflammation. *Id.*; *see also* Ex. 7 at 237, 541. J.T. also had MRIs on June 26, 2012, and January 29, 2014, which were normal. MacGinnitie Rep. at 5; *see also* Ex. 3 at 20-21; Ex. 7 at 604-05. J.T. also had a normal C-reactive protein level on January 12, 2012. MacGinnitie Rep. at 5; *see also* Ex. 1 at 283. According to Suleiman, autoimmune epilepsy would appear in CSF fluid or on an MRI. MacGinnitie Rep. at 5; *see also* Suleiman and Dale, *The recognition and treatment of autoimmune epilepsy in children*, 57 DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY 431-40 (2015) (filed as Ex. 104). J.T. was also never treated with corticosteroids, IVIG, or immunomodulatory treatments. MacGinnitie Rep. at 6.

Regarding one of Dr. Shafrir's theories, Dr. MacGinnitie opined that six to eight hours post-vaccination is too fast for an anamnestic (memory) response. MacGinnitie Rep. at 7. In Pichichero, a study of repeat Hib vaccinations found immune responses four to five days after vaccinations. *Id.*; *see also* Pichichero et al., *Kinetics of Booster Responses to Haemophilus*

*Influenzae Type B Conjugate after Combined Diphtheria-Tetanus-Acellular Pertussis-Haemophilus Influenzae Type b Vaccination in Infants*, 18 PEDIATRIC INFECTIOUS DISEASE JOURNAL 12, 1106-08 (1999) (filed as Ex. I9).

Dr. MacGinnitie also opined that there is no evidence that J.T.'s pathology/Dravet syndrome was a IgE mediated response. MacGinnitie Rep. at 8. Furthermore, the blood brain barrier ("BBB") protects the brain from infectious and toxic attacks; Dr. Shafrir has not offered any theory how the vaccine could breach the BBB. *Id.* at 9. Dr. MacGinnitie stated that "vaccinations can trigger seizures as the first manifestation of Dravet [syndrome], but studies have shown it does not alter the course of the disease." *Id.* at 11. There is no evidence from the testing done on J.T. that Dr. Shafrir's proposed inflammatory/autoimmune mechanism occurred. *Id.* J.T.'s symptoms are better explained by Dravet syndrome caused by the GABRA1 mutation. *Id.*

### 3. Testimony

During the entitlement hearing, Dr. MacGinnitie testified regarding Dr. Shafrir's suggestion in his first expert report that J.T. may have had an IgA deficiency that presented as frequent infections in the first year of life. Tr. at 269. Dr. MacGinnitie opined that, without testing J.T.'s IgA levels, we cannot know whether or not J.T. had an IgA deficiency. *Id.* Dr. Shafrir previously opined that J.T. had an abnormal or overexuberant immune response, possibly due to the IgA deficiency, but J.T.'s development of a fever after the third dose of Pentacel, is consistent with 16% of children. *Id.* at 271-72; Ex. I-12. J.T. was also noted to be irritable, consistent with 68% of children. *Id.* at 272. Dr. MacGinnitie disagreed with Dr. Shafrir's opinion that J.T.'s symptoms indicate an excessive or overexuberant cytokine response to vaccination. *Id.* at 273. Dr. MacGinnitie further opined that J.T.'s symptoms are not consistent with a cytokine storm and that J.T.'s cytokine levels were not high enough to explain his seizures. *Id.* at 273-74. Dr. MacGinnitie also opined that, while vaccines have been known to trigger seizures, there is no evidence that they can lead to a prolonged seizure disorder. *Id.* at 278.

Dr. MacGinnitie also posited that J.T.'s condition is not explained by autoimmunity. Tr. at 279. He stated that the vaccines J.T. received have not been shown to cause an ongoing autoimmune process and that J.T. should show evidence of adaptive immune system involvement for autoimmunity to explain his disease. *Id.*

Dr. MacGinnitie expressed a lack of certainty as a non-neurologist as to whether Dravet syndrome is the correct diagnosis for J.T. Tr. at 285. He disagreed with Dr. Shafrir's opinion that J.T. suffered encephalopathy after his first seizure because J.T. was "'back to normal', you know, within minutes after the seizure." *Id.* at 287.

Regarding J.T.'s developmental regression, Dr. MacGinnitie believed that his appointment on August 31, 2012 and the observations made by Dr. Thio at that appointment did not constitute evidence of regression, but would be a cause for concern. Tr. at 289-90. He noted that he was unable to point to anything in the medical record that J.T. was able to do and later unable to do and pointed out that difference children acquire various skills at different ages. *Id.* at 289. He opined that the "overall picture" of a child's development is more significant than any one specific skill. *Id.* at 290.

## V. Applicable Law

### A. Petitioner's Burden in Vaccine Program Cases

Under the Vaccine Act, when a petitioner suffers an alleged injury that is not listed in the Vaccine Injury Table, a petitioner may demonstrate that he suffered an “off-Table” injury. § 11(c)(1)(C)(ii).

In attempting to establish entitlement to a Vaccine Program award of compensation for a off-Table claim, a petitioner must satisfy all three of the elements established by the Federal Circuit in *Althen v. Sec'y of Health & Hum. Servs.*, 418 F.3d 1274 (Fed. Cir. 2005). *Althen* requires that petitioner establish by preponderant evidence that the vaccination he received caused his injury “by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury.” *Id.* at 1278.

Under the first prong of *Althen*, petitioners must provide a “reputable medical theory,” demonstrating that the vaccine received *can cause* the type of injury alleged. *Pafford*, 451 F.3d at 1355-56 (citations omitted). To satisfy this prong, a petitioner’s theory must be based on a “sound and reliable medical or scientific explanation.” *Knudsen v. Sec'y of Health & Hum. Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). Proof that the proffered medical theory is reasonable, plausible, or possible does not satisfy a petitioner’s burden. *Boatmon v. Sec'y of Health & Hum. Servs.*, 941 F.3d 1351, 1359-60 (Fed. Cir. Nov. 7, 2019).

Petitioners may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu v. Sec'y of Health & Hum. Servs.*, 569 F.3d 1367, 1378-79 (Fed. Cir. 2009) (citing *Capizzano v. Sec'y of Health & Hum. Servs.*, 440 F.3d 1317, 1325-26 (Fed. Cir. 2006)). However, special masters are “entitled to require some indicia of reliability to support the assertion of the expert witness.” *Boatmon*, 941 F.3d at 1360, quoting *Moberly v. Sec'y of Health & Hum. Servs.*, 592 F.3d 1315, 1324 (Fed. Cir. 2010). Special Masters, despite their expertise, are not empowered by statute to conclusively resolve what are complex scientific and medical questions, and thus scientific evidence offered to establish *Althen* prong one is viewed “not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act’s preponderant evidence standard.” *Id.* at 1380. Accordingly, special masters must take care not to increase the burden placed on petitioners in offering a scientific theory linking vaccine to injury. *Contreras v. Sec'y of Health & Hum. Servs.*, 121 Fed. Cl. 230, 245 (2015), vacated on other grounds, 844 F.3d 1363 (Fed. Cir. 2017); see also *Hock v. Sec'y of Health & Hum. Servs.*, No. 17-168V, 2020 U.S. Claims LEXIS 2202 at \*52 (Fed. Cl. Spec. Mstr. Sept. 30, 2020).

The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner’s medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375-77; *Capizzano*, 440 F.3d at 1326 (“medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a ‘logical sequence of cause-and-effect show[s] that the vaccination was the

reason for the injury'') (quoting *Althen*, 418 F.3d at 1280). Medical records are generally viewed as particularly trustworthy evidence, since they are created contemporaneously with the treatment of the patient. *Cucuras v. Sec'y of Health & Hum. Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993).

However, medical records and/or statements of a treating physician's views do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. Section 13(b)(1) (providing that “[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court”). As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases. The views of treating physicians should also be weighed against other, contrary evidence also present in the record. *Hibbard v. Sec'y of Health & Hum. Servs.*, 100 Fed. Cl. 742, 749 (2011), *aff'd*, 698 F.3d 1355 (Fed. Cir. 2012); *Caves v. Sec'y of Health & Hum. Servs.*, No. 06-522V, 2011 WL 1935813, at \*17 (Fed. Cl. Spec. Mstr. Apr. 29, 2011), *mot. for review den'd*, 100 Fed. Cl. 344, 356 (2011), *aff'd without opinion*, 475 Fed. App'x 765 (Fed. Cir. 2012).

The third *Althen* prong requires establishing a “proximate temporal relationship” between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase “medically-acceptable temporal relationship.” *Id.* A petitioner must offer “preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder’s etiology, it is medically acceptable to infer causation.” *de Bazan v. Sec'y of Health & Hum. Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one’s requirement). *Id.* at 1352; *Shapiro v. Sec'y of Health & Hum. Servs.*, 101 Fed. Cl. 532, 542 (2011), *recons. den'd after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem.*, 503 F. App'x 952 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Hum. Servs.*, No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review den'd* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

The Vaccine Act defines significant aggravation as “any change for the worse in a preexisting condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration of health.” § 300aa-33(4). In *Loving*, the United States Court of Federal Claims established the governing six-part test for off-Table significant aggravations. Petitioner must prove by a preponderance of the evidence:

- (1) The person’s condition prior to administration of the vaccine, (2) the person’s current condition (or the condition following the vaccination if that is also pertinent), (3) whether the person’s current condition constitutes a ‘significant aggravation’ of the person’s condition prior to vaccination, (4) a medical theory causally connecting such a significant worsened condition to the vaccination, (5) a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation, and (6) a showing of a proximate temporal relationship between the vaccination and the significant aggravation.

*Loving v. Sec'y of Health & Hum. Servs.*, 86 Fed. Cl. 135, 144 (2009); *see also W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1357 (Fed. Cir. 2013) (adopting this as the proper legal

standard for significant aggravation claims brought under the Vaccine Act). *Loving* prongs four, five, and six are derived from the Federal Circuit’s test for off-Table actual causation cases. *Althen v. Sec’y of Health & Hum. Servs.*, 17 F.3d 374 (Fed. Cir. 1994).

In *Sharpe*, the Federal Circuit clarified the *Loving* prongs and what is required by petitioners to successfully demonstrate a causation-in-fact significant aggravation claim. *Sharpe v. Sec’y of Health & Hum. Servs.*, 964 F.3d 1072 (Fed. Cir. 2020). *Loving* prong three only requires a comparison of a petitioner’s current, post-vaccination condition with his pre-existing pre-vaccination condition. *Sharpe* at 1082; *Whitecotton v. Sec’y of Health & Hum. Servs.*, 81 F.3d 1099 (Fed. Cir. 1996). A petitioner is not required to demonstrate an expected outcome or that his post-vaccination condition was worse than such an expected outcome. *Sharpe* at 1081. Further, a petitioner is not required “to disprove that a pre-existing genetic mutation caused [his] significant aggravation.” *Sharpe* at 1087.

Under *Loving* prong four, a petitioner need only provide a “medical theory causally connecting [petitioner’s] significantly worsened condition to the vaccination.” *Sharpe* at 1083; *see also Loving*, 86 Fed. Cl. at 144. In other words, petitioner is required to present a medically reliable theory demonstrating that a vaccine “can cause a significant worsening” of the condition. *Sharpe* at 1083 (citing to *Pafford ex. rel. Pafford v. Sec’y of Health & Hum. Servs.*, 451 F.3d 1352, 1356-57 (Fed. Cir. 2006)). A petitioner may be able to establish a *prima facie* case under *Loving* prong four without eliminating a pre-existing condition as the cause of her significantly aggravated injury. *Id.*; citing *Walther v. Sec’y of Health & Hum. Servs.*, 485 F.3d 1146, 1151 (Fed. Cir. 2007) (noting that “the government bears the burden of establishing alternative causation. . . . once petitioner has established a *prima facie* case”).

*Loving* prong five requires a petitioner to show “a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation.” *Loving*, 86 Fed. Cl. at 144. In other words, petitioner must show that the vaccinations “did” cause a worsening of [petitioner’s underlying disorder]. *Id.*

In determining whether a petitioner is entitled to compensation, a special master must consider the entire record and is not bound by any particular piece of evidence. § 13(b)(1) (stating that a special master is not bound by any “diagnosis, conclusion, judgment, test result, report, or summary” contained in the record). Furthermore, a petitioner is not required to present medical literature or epidemiological evidence to establish any *Althen* prong. The special master essentially must weigh and evaluate opposing evidence in deciding whether a petitioner has met their burden of proof. *Andreu v. Sec’y of Health & Hum. Servs.*, 569 F.3d 1367, 1380 (Fed. Cir. 2009); *see also Grant v. Sec’y of Health & Hum. Servs.*, 956 F.2d 1144, 1149 (Fed. Cir. 1992).

## B. Law Governing Analysis of Fact Evidence

The process for making factual determinations in Vaccine Program cases begins with analyzing the medical records, which are required to be filed with the petition. Section 11(c)(2). The special master is required to consider “all [] relevant medical and scientific evidence contained in the record,” including “any diagnosis, conclusion, medical judgment, or autopsy or coroner’s report which is contained in the record regarding the nature, causation, and aggravation of the

petitioner's illness, disability, injury, condition, or death," as well as the "results of any diagnostic or evaluative test which are contained in the record and the summaries and conclusions." Section 13(b)(1)(A). The special master is then required to weigh the evidence presented, including contemporaneous medical records and testimony. *See Burns v. Sec'y of Health & Hum. Servs.*, 3 F.3d 413, 417 (Fed. Cir. 1993) (it is within the special master's discretion to determine whether to afford greater weight to contemporaneous medical records than to other evidence, such as oral testimony surrounding the events in question that was given at a later date, provided that such determination is evidenced by a rational determination).

Medical records created contemporaneously with the events they describe are generally trustworthy because they "contain information supplied to or by health professionals to facilitate diagnosis and treatment of medical conditions," where "accuracy has an extra premium." *Kirby v. Sec'y of Health & Hum. Servs.*, 997 F.3d 1378 (Fed. Cir. 2021) citing *Cucuras*, 993 F.2d at 1528. This presumption is based on the linked proposition that (i) sick people visit medical professionals; (ii) sick people honestly report their health problems to those professionals; and (iii) medical professionals record what they are told or observe when examining their patients in as accurate a manner as possible, so that they are aware of enough relevant facts to make appropriate treatment decisions. *Sanchez v. Sec'y of Health & Hum. Servs.*, No. 11-685V, 2013 WL 1880825 at \*2 (Fed. Cl. Spec. Mstr. Apr. 10, 2013) *mot. for rev. denied*, 142 Fed. Cl. 247, 251-52 (2019), *vacated on other grounds and remanded*, 809 Fed. Appx. 843 (Fed. Cir. Apr. 7, 2020).

Accordingly, if the medical records are clear, consistent, and complete, then they should be afforded substantial weight. *Lowrie v. Sec'y of Health & Hum. Servs.*, No. 03-1585V, 2005 WL 6117475 at \*20 (Fed. Cl. Spec. Mstr. Dec. 12, 2005). Indeed, contemporaneous medical records are generally found to be deserving of greater evidentiary weight than oral testimony -- especially where such testimony conflicts with the record evidence. *Cucuras*, 993 F.2d at 1528; see also *Murphy v. Sec'y of Health & Hum. Servs.*, 23 Cl. Ct. 726, 733 (1991), *aff'd per curiam*, 968 F.2d 1226 (Fed. Cir. 1992), *cert. den'd*, *Murphy v. Sullivan*, 506 U.S. 974 (1992) (citing *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 396 (1947) ("[i]t has generally been held that oral testimony which is in conflict with contemporaneous documents is entitled to little evidentiary weight.")).

However, there are situations in which compelling oral testimony may be more persuasive than written records, such as where records are deemed to be incomplete or inaccurate. *Campbell v. Sec'y of Health & Hum. Servs.*, 69 Fed. Cl. 775, 779 (2006) ("like any norm based upon common sense and experience, this rule should not be treated as an absolute and must yield where the factual predicates for its application are weak or lacking"); *Lowrie*, 2005 WL 6117475 at \*19 ("[w]ritten records which are, themselves, inconsistent, should be accorded less deference than those which are internally consistent") (quoting *Murphy*, 23 Cl. Ct. at 733)). Ultimately, a determination regarding a witness's credibility is needed when determining the weight that such testimony should be afforded. *Andrew*, 569 F.3d at 1379; *Bradley v. Sec'y of Health & Hum. Servs.*, 991 F.2d 1570, 1575 (Fed. Cir. 1993).

When witness testimony is offered to overcome the presumption of accuracy afforded to contemporaneous medical records, such testimony must be "consistent, clear, cogent and compelling." *Sanchez*, 2013 WL 1880825 at \*3 (citing *Blutstein v. Sec'y of Health & Hum. Servs.*, No. 90-2808V, 1998 WL 408611 at \*5 (Fed. Cl. Spec. Mstr. June 30, 1998)). In determining the

accuracy and completeness of medical records, the Court of Federal Claims has listed four possible explanations for inconsistencies between contemporaneously created medical records and later testimony: (1) a person's failure to recount to the medical professional everything that happened during the relevant time period; (2) the medical professional's failure to document everything reported to her or him; (3) a person's faulty recollection of the events when presenting testimony; or (4) a person's purposeful recounting of symptoms that did not exist. *LaLonde v. Sec'y of Health & Hum. Servs.*, 110 Fed. Cl. 184, 203-04 (2013), *aff'd*, 746 F.3d 1334 (Fed. Cir. 2014). In making a determination regarding whether to afford greater weight to contemporaneous medical records or other evidence, such as testimony at hearing, there must be evidence that this decision was the result of a rational determination. *Burns*, 3 F.3d at 417.

### C. Analysis of Expert Testimony

Establishing a sound and reliable medical theory connecting the vaccine to the injury often requires petitioners to present expert testimony in support of their claim. *Lampe v. Sec'y of Health & Hum. Servs.*, 219 F.3d 1357, 1361 (Fed. Cir. 2000). Vaccine Program expert testimony is usually evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 594-96 (1993). See *Cedillo v. Sec'y of Health & Hum. Servs.*, 617 F.3d 1328, 1339 (Fed. Cir. 2010) (*citing Terran v. Sec'y of Health & Hum. Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999)). “The *Daubert* factors for analyzing the reliability of testimony are: (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community.” *Terran*, 195 F.3d at 1316 n.2 (*citing Daubert*, 509 U.S. at 592-95).

The *Daubert* factors play a slightly different role in Vaccine Program cases than they do when applied in other federal judicial fora. *Daubert* factors are employed by judges to exclude evidence that is unreliable and potentially confusing to a jury. In Vaccine Program cases, these factors are used in the weighing of the reliability of scientific evidence. *Davis v. Sec'y of Health & Hum. Servs.*, 94 Fed. Cl. 53, 66-67 (2010) (“uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted”).

Respondent frequently offers one or more experts of his own in order to rebut petitioners’ case. Where both sides offer expert testimony, a special master’s decision may be “based on the credibility of the experts and the relative persuasiveness of their competing theories.” *Broekelschen v. Sec'y of Health & Hum. Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (*citing Lampe*, 219 F.3d at 1362). However, nothing requires the acceptance of an expert’s conclusion “connected to existing data only by the *ipse dixit* of the expert,” especially if “there is simply too great an analytical gap between the data and the opinion proffered.” *Snyder*, 88 Fed. Cl. at 743 (*quoting Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)). A “special master is entitled to require some indicia of reliability to support the assertion of the expert witness.” *Moberly*, 592 F.3d at 1324. Weighing the relative persuasiveness of competing expert testimony, based on a particular expert’s credibility, is part of the overall reliability analysis to which special masters

must subject expert testimony in Vaccine Program cases. *Id.* at 1325-26 (“[a]ssessments as to the reliability of expert testimony often turn on credibility determinations”).

#### **D. Consideration of Medical Literature**

Although this decision discusses some but not all of the medical literature in detail, I reviewed and considered all of the medical records and literature submitted in this matter. *See Moriarty v. Sec'y of Health & Hum. Servs.*, 844 F.3d 1322, 1328 (Fed. Cir. 2016) (“We generally presume that a special master considered the relevant record evidence even though [s]he does not explicitly reference such evidence in h[er] decision.”); *Simanski v. Sec'y of Health & Hum. Servs.*, 115 Fed. Cl. 407, 436 (2014) (“[A] Special Master is ‘not required to discuss every piece of evidence or testimony in her decision.’” (citation omitted)), *aff'd*, 601 F. App'x 982 (Fed. Cir. 2015).

### **VI. Analysis**

Because Petitioners do not allege an injury listed on the Vaccine Injury Table, their claim is classified as “off-Table.” As noted above, to prevail on an “off-Table” claim, Petitioners must prove by preponderant evidence that J.T. suffered an injury and that this injury was significantly aggravated by the vaccination at issue. *See Capizzano*, 440 F.3d at 1320.

#### **A. EIEE19, Dravet Syndrome, GABRA1 Variant**

“Early infantile epileptic encephalopathy (EIEE) is a diverse group of clinical disorders that are characterized by early-onset seizures with developmental issues.” First Raymond Rep. at 5. Many EIEEs have genetic causes. *Id.*

Dravet syndrome is a type of EIEE and is a severe epilepsy that begins in infancy. First Raymond Rep. at 5; Catarino et al. stated that Dravet syndrome is “characterized by onset of recurrent febrile and/or afebrile hemiclonic or generalized seizures, or status epilepticus, in a previously healthy infant, followed by appearance of multiple seizure types generally resistant to anti-epileptic drugs with developmental arrest or regression.” Catarino et al., *Dravet syndrome as epileptic encephalopathy: evidence from long-term course and neuropathology*, 134 BRAIN 2982-3010, at 2983 (2011) (filed as Ex. 158). Dravet syndrome is a clinical diagnosis. First Raymond Rep. at 5.

Dravet syndrome is uncommon, and has an estimated incidence of <1:40,000 children. Catarino at 2983. Of this small percentage of the population that develops Dravet syndrome, between 70-80% of those cases are caused by an SCN1A variant. *Id.* Carvill et al. performed whole-exome sequencing in SCN1A-negative patients with Dravet syndrome and discovered that the GABRA1 gene also has an association with DS. Carvill et al., *GABRA1 and STXBP1: Novel genetic causes of Dravet syndrome*, 82 NEUROLOGY 1245-53 (2014) (filed as Ex. 60).

The Online Mendelian Inheritance of Man (OMIM) is a catalog of human genes and their disorders. Second Raymond Rep. at 1. “Severe disease resulting from SCN1A is labeled as EIEE6

(OMIM 607208) and the clinically similar condition due to variants in GABRA1 is entitled EIEE19 (OMIM 615744).” *Id.*

Dr. Raymond testified at the entitlement hearing that “J.T. is a child with an early infantile epileptic encephalopathy... [I]f you were just looking for the diagnostic label, he would be considered EIEE19, secondary to a GABRA1 mutation or variant, and he’s been clinically diagnosed as having Dravet syndrome.”<sup>5</sup> Tr. at 301. Specifically, J.T. has a *de novo* L215V mutation in the GABRA1 gene. Ex. 10 at 26-30. “The change in nucleotide bases from guanine to cytosine at position 643 results in a transition from the amino acid leucine to the amino acid valine at position 215 in the resultant GABRA1 protein.” First Raymond Rep. at 5.

## B. *Loving* Analysis

This case involves a previously asymptomatic child who developed a seizure disorder post vaccination. Genetic sequencing later identified a genetic basis for his condition. In cases such as this, it is typical for special masters to conduct a *Loving* analysis, and to treat the genetic variant as a pre-existing condition. Although many diseases have a genetic component, and some even have a pre-clinical phase (like seropositive RA), special masters use a causation in fact framework to analyze Vaccine Act claims involving these other diseases. However, whether I analyze this case pursuant to *Althen* or *Loving*, the end result is the same. See *Barclay v. Sec'y of Health & Hum. Servs.*, 122 Fed. Cl. 189, 193 (2015) (discussing the complexity of a significant aggravation analysis when addressing a latent pre-existing condition).

### 1. *Loving* Prong One: J.T.’s Condition prior to the July 7, 2012 DTaP Vaccination

J.T. developed normally before he received the DTaP component of his Pentacel vaccine on July 7, 2012. His six month well child visit was a routine exam where J.T. was noted to be vocal, sociable, well developed, and well nourished. Ex. 2 at 203. Dr. Fleischer directed Mrs. Thompson to return with J.T. in three months for his next routine wellness visit. *Id.*

### 2. *Loving* Prong Two: J.T.’s Condition after the July 7, 2012 DTaP Vaccination

J.T. had a seizure on July 7, 2012, within six to eight hours of receiving his Pentacel vaccine. As discussed in detail in section VI(B)(5)(b), J.T.’s development then began to plateau. Petitioners brought J.T. to a medical appointment on August 31, 2012 because they were concerned about his development. He had four seizures on September 11, 2012. An EEG performed on September 17, 2012 documented “the occurrence of high voltage spike and slow wave activity seen in the left frontal temporal region, especially during drowsiness.” Ex. 8 at 1413. Over the course of the next several years, J.T. began having different types of seizures, sometimes as many as 20 per hour. Ex. 7 at 568-82. As of the date of the hearing, J.T. was nine years old. He could speak fewer than 10 words, was not potty trained, and could not feed or dress himself.

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<sup>5</sup> The parties extensively discussed J.T.’s condition and whether Dravet syndrome is his correct diagnosis. Ultimately, I find that the record supports that DS is J.T.’s clinical diagnosis. For that reason, I describe J.T. as having EIEE19 and Dravet syndrome throughout this Ruling.

3. *Loving* Prong Three: Did J.T. Experience a Significant Aggravation of his Condition?

J.T.’s deterioration is consistent with the Vaccine Act’s definition of significant aggravation resulting in markedly greater disability, pain, or illness accompanied by substantial deterioration of health. § 33(4). Therefore, this leaves the question of whether the significant aggravation of J.T.’s condition was vaccine-related.

4. *Loving* Prong Four/*Althen* Prong One

Under *Loving* prong four/*Althen* prong one, the causation theory must relate to the injury alleged. Thus, Petitioners must provide a “reputable” medical or scientific explanation, demonstrating that the vaccines received can cause a significant aggravation of the type of injury alleged. *Pafford*, 451 F.3d at 1355-56. The theory must be based on a “sound and reliable medical or scientific explanation.” *Knudsen v. Sec’y of Health & Hum. Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). It must only be “legally probable, not medically or scientifically certain.” *Id.* at 549.

Dr. Shafrir offered several different causation theories in this case. I have focused on the one that I find persuasive: J.T. had an abnormal reaction to vaccination due to his preexisting genetic susceptibility. Fourth Shafrir Rep. at 16. The DTaP vaccine caused the release of proinflammatory cytokines which impacted the blood brain barrier and caused J.T. to have a febrile seizure. First Shafrir Rep. at 54. This seizure damaged his brain and resulted in developmental stagnation. Tr. at 72. The perpetuation of J.T.’s condition was caused by an “onset of the cascade of events that led to [an] irreversible situation in the brain and persistence of epileptic encephalopathy that otherwise would not have occurred.” *Id.* at 151.

a. *DTaP Vaccine Can Cause Febrile Seizures in a Genetically-Susceptible Host*

At the outset, I note that special masters in the Vaccine Program have determined that vaccination can cause febrile seizures and subsequent damage to the brain either in the form of a seizure disorder or an encephalopathy. *See, e.g., Weaver v. Sec’y of Health & Hum. Servs.*, No. 16-1494, 2022 WL 12542485, at \*24-25 (Fed. Cl. Spec. Mstr. Sep. 23, 2022) (concluding that under some circumstances, a vaccine-induced febrile seizure could cause a seizure disorder, and emphasizing the importance of evidence demonstrating that the child’s brain was damaged by the initial febrile seizure); *Ginn v. Sec’y of Health & Hum. Servs.*, No. 16-1466, 2021 WL 1558342, at \*6 (Fed. Cl. Spec. Mstr. Mar. 26, 2021) (finding that “a brief febrile seizure triggered by vaccinations can be the starting point for the development of epilepsy.”); *Fuller v. Sec’y of Health & Hum. Servs.*, No. 15-1470V, 2019 WL 757638, at \*16 (Fed. Cl. Spec. Mstr. Dec. 17, 2019) (finding that DTaP vaccine caused child’s febrile seizure and ensuing seizure disorder); *Tembenis v. Sec’y of Health & Hum. Servs.*, No. 03-2820V, 2010 WL 5164324, at \*15-16 (Fed. Cl. Spec. Mstr. Nov. 29, 2010) (finding entitlement where child experienced febrile seizure following DTaP vaccination, which resulted in epilepsy and child’s subsequent death). *Johnson v. Sec’y of Health & Hum. Servs.*, No. 07-138V, 2010 WL 3291932, \*15 (Fed. Cl. Spec. Mstr. July 30, 2010) (accepting Dr. Shafrir’s opinion that DTaP and other vaccines caused febrile seizure and encephalopathy); *see also Romero v. Sec’y of Health & Hum. Servs.*, No. 07-671V, 2010 WL

2766761, \*15 (Fed. Cl. Spec. Mstr. June 22, 2010) (concluding that DTaP reduces but does not eliminate the incidence of uncommon adverse events such as seizures).

During the entitlement hearing, Dr. Shafrir testified that the DTaP vaccine can cause immune dysregulation, specifically an increase in the production of proinflammatory cytokines which “can have an effect on the blood brain barrier and penetrate into the brain...” Tr. at 64. Dr. Shafrir’s position is supported by medical literature filed in the case. For example, the Sun article concluded that “DTaP-IPV-Hib vaccination was associated with an increased risk of febrile seizures on the day of the first 2 vaccinations given at 3 and 5 months, although the absolute risk was small.” Sun et al., *Risk of Febrile Seizures and Epilepsy After Vaccination With Diphtheria, Tetanus, Acellular Pertussis, Inactivated Poliovirus, and Haemophilus Influenzae Type b*, 307 JAMA 8, 823-31 (2012)(filed as Ex. 148). I also note that Dr. MacGinnitie agreed with Dr. Shafrir on this point. He testified “there’s clearly evidence [the DTaP vaccine] can cause ... febrile seizures in Dravet.” Tr. at 284. Accordingly, this issue is not meaningfully disputed.

#### b. *Seizures Can Cause Encephalopathy*

Respondent summarized Dr. Shafrir’s theory in his brief: “secondary changes in the brain caused by the initial seizure could cause seizures to persist and worsen.” Resp’t’s Brief at 30.<sup>6</sup> As Dr. Shafrir testified at the entitlement hearing, “it could very well be that the initial seizure already sealed his fate...” Tr. at 72.

Dr. Shafrir cited Zielinski and Rosinska, a Polish epidemiological study which examined the rate of systemic adverse reactions following the whole-cell DTP vaccine compared with its acellular counterpart. Zielinski and Rosinska found that adverse reactions followed both vaccines, but that they occurred twice as frequently after receipt of whole-cell DTP. Andrzej Zielinski and Magdalena Rosinska, *Comparison of Adverse Effects Following Immunization with Vaccine Containing Whole-Cell Versus Acellular Pertussis Components*, 62 PRZEGŁ EPIDEMIOL 589-96 (2008) (filed as Ex. 83) (hereinafter “Zielinski and Rosinska”). The authors opined that the higher rates of seizures following DTP vaccine could be due to increased rates of fever because “[f]ebrile reactions were more than twice as frequent among children receiving whole cell vaccine.” Zielinski and Rosinska at 594. As Special Master Gowen noted in *Morales*, this study “has previously been accepted for the proposition that acellular pertussis toxoid vaccine still carries risk for neurological injury including encephalopathy.” *Morales v. Sec’y Health & Hum. Servs.*, No. 14-1186V, 2019 WL 4047626, at \*12 (Fed. Cl. Spec. Mstr. July 30, 2019), citing *Johnson v. Sec’y of Health & Hum. Servs.*, No. 07-138V, 2010 WL 3291932, at \*15 (Fed. Cl. Spec. Mstr. July 30, 2010). Ultimately, the Zielinski and Rosinska paper provides additional support for Dr. Shafrir’s theory that the DTaP vaccine can cause damage to the brain.

The paper by Cetica et al. also supports this point. The authors note that “earlier onset of seizure activity can actually by itself induce changes that permanently lower seizure threshold and cause cognitive impairment, above and beyond what is caused by the underlying mutation.” Cetica

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<sup>6</sup> Respondent further stated that “Dr. Shafrir did not point to any evidence in the records that supported his supposition that J.C.T. suffered changes to his brain as the result of his first seizure.” Resp’t’s Brief at 30, fn. 28. I disagree with this assertion, and have analyzed this issue under Loving Prong five.

et al., *Clinical and genetic factors predicting Dravet syndrome in infants with SCN1A Mutations*, 88 NEUROLOGY, 1037-44, at 1043 (2017) (filed as Ex. 105) (hereinafter “Cetica”). Cetica reinforces the point that an initial seizure, especially one that occurs when an infant is six months of age or younger, can cause damage to the brain that begets additional seizures.

Verbeek et al. studied the effect of vaccine-associated seizure onset on disease course in Dravet syndrome. Verbeek concluded that although vaccination results in earlier seizure onset in DS, this earlier onset “does not alter disease course...” Verbeek et al., *Effects of Vaccinations on seizure risk and disease course in Dravet syndrome*, 85 NEUROLOGY 596-603, (2015) (filed as Ex. I5) (hereinafter “Verbeek”). However, Verbeek cautioned that “seizures in DS in general may progress to status epilepticus, which may, in some patients, lead to acute encephalopathy with severe neurologic deterioration, and this might also apply to vaccination-associated seizures. Therefore, precautions to reduce vaccination-associated seizure risk such as use of vaccines with lower seizure risk when available, should be considered.” Verbeek at 602. While J.T. did not develop status epilepticus after his July 7, 2012 DTaP vaccine, this statement suggests that an initial vaccine-induced febrile seizure can cause an encephalopathy.

Ultimately, Dr. Shafrir’s expert opinion that the DTaP vaccine can cause a febrile seizure which in turn can cause damage to the brain is supported by the medical literature filed in this case. Petitioners have presented preponderant evidence in support of the fourth *Loving* prong.

##### 5. Loving Prong Five/Althen Prong Two

*Loving* prong five/*Althen* prong two requires the Petitioners to provide a logical sequence of cause and effect demonstrating that vaccination did cause a worsening of J.T.’s pre-existing condition. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375-77; *Grant*, 956 F.2d at 1148.

###### a. *J.T. Experienced a Seizure 6-8 Hours after Pentacel Vaccine*

It is uncontested that J.T. experienced a seizure the same day he received the DTaP component of his Pentacel vaccine. J.T. had his six month well child exam on July 7, 2012. He suffered a seizure at around 8:30-8:45pm that evening. Ex. 1 at 13, 26. Although the time of the wellness exam is not documented in the records, Dr. Thio noted that J.T. “had his first seizure 6 to 8 hours after receiving a vaccination including pertussis.” Ex. 8 at 15.

Several of J.T.’s treating physicians believe his vaccination caused this initial seizure. The ER doctor diagnosed J.T. with “febrile seizure, [f]ollowing vaccines today.” Ex. 1 at 14. Dr. Fleischer noted “[d]ifferential of febrile seizure, probably fever due to yesterday’s immunizations vs. syncopal or breath-holding spell.” Ex. 1 at 16. Dr. Devinsky opined that the July 7, 2012 DTaP vaccine “activated” J.T.’s epilepsy. Ex. 24. Additionally, Dr. MacGinnitie testified that it is “possible” that J.T.’s DTaP vaccination caused his seizure on July 7, 2012. Tr. at 284. Based on the above, I find Petitioners have presented preponderant evidence that J.T.’s July 7, 2012 DTaP vaccination did cause his initial seizure, which constituted the onset of his Dravet syndrome.<sup>7</sup>

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<sup>7</sup> Dr. Charlotte Dravet noted that “Dravet syndrome begins during the first year of life in a normal baby who presents with one convulsive seizure, related or not to fever or vaccination.” Charlotte Dravet, *The core Dravet syndrome phenotype*, 52 EPILEPSIA (Suppl. 2) at 4 (2011) (filed as Ex. F1) (hereinafter “C.

b. *Developmental Regression or Plateauing*

Central to Petitioners' theory is that J.T.'s brain changed after his initial seizure. Petitioners find support for their position in J.T.'s medical records.

Petitioners contend that J.T. regressed, that he lost developmental milestones he previously possessed after his initial seizure on July 7, 2012. Respondent asserts instead that J.T. merely plateaued, and that the plateauing did not begin until after his seizures on September 11, 2012. Tr. at 355. Whether J.T.'s development is described as a regression or a plateauing is not significant in my assessment of whether J.T.'s vaccine "did cause" a significant aggravation of his condition. In defining Dravet syndrome, Catarino et al. stated "Dravet syndrome is characterized by onset of recurrent febrile and/or afebrile hemiclonic or generalized seizures, or status epilepticus, in a previously healthy infant, followed by appearance of multiple seizure types generally resistant to anti-epileptic drugs with developmental arrest or regression." Catarino at 2 (emphasis added). This statement indicates that a child who develops Dravet syndrome will experience either regression or developmental arrest. McIntosh reinforces this point; the authors note "From the second year of life, intellectual development in these infants begins to plateau or regress, resulting in intellectual disability." McIntosh at 592 (emphasis added).

Accordingly, the question is not whether J.T. experienced a regression or a plateauing in his development, but when this occurred. This question is a difficult one. This difficulty is, in part, due to the fact that any loss of skills or stagnation in development may take place over a period of time, and not immediately. While this is true in J.T.'s case, I find that preponderant evidence supports the delay in development began after the July 7, 2012 seizure and before his next seizures on September 11, 2012.

Before his seizures, J.T.'s development was normal. J.T. presented for his six-month well visit on July 7, 2012. His pediatrician noted that he was "vocal", that he "bears w[eigh]t", he had "good head control", and he was noted to be "sociable". Ex. 2 at 203. Dr. Fleischer documented that he was well developed and well nourished. *Id.* J.T. was administered his vaccines and directed to return in three months for his routine nine-month well exam. *Id.*

J.T. had a seizure that same day that lasted for five to ten minutes. Ex. 8 at 1402. He had a fever measured at 39.3°C (102.7°F). Ex. 2 at 204. There is no documented regression or change in his mental status in the days following this seizure.

However, on August 31, 2012, Petitioners brought J.T. to see Dr. Fleischer for a developmental consultation. Ex. 2 at 204. This was not a regular well exam, but Petitioners scheduled it because they were concerned about J.T.'s development. J.T. was eight months old at the time of this appointment. Petitioners noted that J.T. was vocal but was not babbling. *Id.* He

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Dravet"). This means that the first seizure constitutes the onset of Dravet syndrome. Dr. Raymond noted in his first expert report that McIntosh also "defined the onset of Dravet syndrome as the first seizure." First Raymond Rep. at 8.

rolls but was not sitting independently and he was not crawling. *Id.* The record notes “not finger foods” indicating that he was not feeding himself. *Id.* Dr. Fleischer documented that the exam was normal. *Id.* However, at hearing, Dr. Shafrir testified that a child who cannot feed himself at eight months of age is not developing normally. He described such a child as “developmentally delayed” opining, “It’s clearly abnormal.” Tr. at 197.

Dr. MacGinnitie also addressed this point. I asked him whether he would be concerned if Petitioners in fact told Dr. Fleischer that J.T. was unable to feed himself. Tr. at 289. Dr. MacGinnitie responded as follows:

And so just seeing this, yes, that would raise my concern, but if I went through an entire screening and the patient was doing fine, I think I would say, like, look, you know, different kids develop different skills at different rates. There are some kids who are late to talk but otherwise normal, others for whom being late to talk indicates profound delay, and so I think I would have to go with the overall picture rather than any specific example.

*Id.* at 290. Although an inability to finger feed, when taken by itself, may not signify a delay in development, when placed in the context of this case it does not appear to be an isolated finding. At later medical appointments, J.T. displayed delays in motor development that Petitioners first complained of during this particular medical visit. These concerns include his speech (not babbling), his inability to sit independently, and his lack of initiating crawling movements. Several later medical visits further discuss J.T.’s inability to use his thumbs effectively, and describe his grasp as “raking”. These later records support the point that the inability to finger feed is linked to a lack of development of J.T.’s fine motor skills.

On September 11, 2012, J.T. experienced two back-to-back “episodes of limpness,” each lasting 30 to 60 seconds, during which his eyes “deviated to the right.” Ex. 4 at 93.

J.T. had an EEG on September 17, 2012. The EEG was interpreted as abnormal “due to the occurrence of high voltage spike and slow wave activity seen in the left frontal temporal region, especially during drowsiness.” Ex. 8 at 1413. The record further notes “[t]his is a specific focal epileptiform abnormality which has a high correlation with clinical seizures. The location of the spike and wave discharges in the left frontal temporal region suggests possible site of origin for seizure.” *Id.*

J.T. had an appointment with Dr. Thio, a neurologist, on November 9, 2012. He was a little older than 10 months of age at this appointment. During this visit, Mr. Thompson raised concerns that J.T. had lost some developmental milestones. The medical record notes Mr. Thompson’s concerns:

Before his seizures started, he was able to sit. He was also starting to make crawling movements. Presently, he is unable to sit on his own well. He had the strength to stand up, which his father believes he no longer has. He now makes no attempt at crawling. Currently, he does not say any words. He does not babble. He started cooing at 2 to 3 months and continues to coo. He does not pull to stand. He does

not wave bye bye or play peek a boo. He does not have a pincer, but he transfers. He has a raking grasp. He is starting to hold a bottle now. He also was not interacting with his parents as well after the seizures, but his ability to interact has improved. He continues to smile and recognize his parents.

Ex. 8 at 1403. During J.T.’s physical examination, Dr. Thio documented that J.T. was alert and very interactive. *Id.* He bore weight on his legs and sat without support. *Id.* Dr. Thio noted that the remainder of the neurologic examination was normal except that J.T. had “mild axial and appendicular hypotonia.” *Id.* At hearing, Dr. Raymond testified that this means J.T. had less tone in the trunk and the limbs than he would expect to see in an average 10 month old. Tr. at 357.

The fact that J.T. does not have a pincer and that he uses a raking grasp generally supports the point from the August 31 record that J.T. was not able to finger feed himself. Further, at ten months of age, J.T. still does not babble, and he does not attempt to crawl.

In summarizing his findings, Dr. Thio stated that J.T.’s “neurological development is remarkable for having lost some motor milestones since the seizures began.” Ex. 8 at 1403 (emphasis added). Dr. Raymond testified at hearing that in his opinion, Dr. Thio’s assessment is not consistent with regression. Tr. at 378-79. However, Dr. Thio’s assessment speaks for itself. In his opinion, J.T. lost milestones “since the seizures began.”

On January 4, 2013, J.T. presented for an initial feeding evaluation. Ex. 8 at 1394. He was one year old at this appointment. The history notes that J.T. had been sitting independently since November, but that he was unstable and would lose his balance. *Id.* at 1394-95. J.T. was able to roll from his stomach to his back. *Id.* at 1395. Mrs. Thompson reported that “prior to the seizures, J.T. took a variety of foods without difficulty, but now prefers only rice cereal.” *Id.* Ms. Cherradi summarized J.T.’s motor skills as follows:

[J.T.] demonstrated lower muscle tone and significant fine and gross motor delay. [J.T.] is able to ring sit with occasional cues for balance. Posterior pelvic tilt was noted in the sitting position. He has difficulty reaching beyond his base of support and demonstrates very little trunk rotation from sitting. [J.T.] needs assistance to go supine to and from sitting. [J.T.] demonstrates a raking grasp of smaller objects. He does not have efficient use of his thumb at this time, and he appears to have some difficulty with thumb abduction and CMC extension.<sup>8</sup> [J.T.] was not able to demonstrate finger isolation for poking or pointing. He is able to transfer toys from hand-hand at midline, but is unable to bang toys together or clap his hands. Overall, [J.T.] seems to demonstrate fine and gross motor skills at about the 6 month level.

*Id.* In addition, Ms. Cherradi observed that J.T. did not babble syllable strings. *Id.* She opined that his receptive and expressive language skills “although delayed for his age, appear to be commensurate with his gross and fine motor skills.” *Id.* at 1396. This visit demonstrates that as J.T. aged, his inability to perform certain skills became more and more outside the norm. Although it does not appear that J.T. had lost any skills, he was clearly not developing normally as of the

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<sup>8</sup> The CMC is the carpometacarpal joint, which is at the base of the thumb where the thumb meets the hand. See Dorland’s, *joint*, [www.dorlandsonline.com/dorland/definition?id=26600](http://www.dorlandsonline.com/dorland/definition?id=26600) (last accessed Nov. 7, 2022).

date of this visit. Many of the concerns that Petitioners raised at the August 31 developmental assessment when J.T. was eight months old were still problems for J.T. on January 4, 2013. J.T. was unable to sit independently without “cues for balance.” He did not have a pincer grasp. He did not have any words and did not babble.

At a May 3, 2013 neurology appointment with Dr. Thio and Dr. Merveen Appu (a child neurology fellow), Drs. Thio and Appu documented that J.T. “does not seem to have made any developmental progress since the onset of seizures.” Ex. 8 at 1390 (emphasis added). This record suggests that J.T. continued developing normally until he was about six months of age, and then his development essentially stopped. Dr. MacGinnitie agreed that J.T. did not meet any developmental milestones after six months of age. Tr. at 288.

During the entitlement hearing, Dr. Shafrir described J.T. as experiencing a “stagnation in development” after his July 7, 2012 vaccine-induced seizure. Tr. at 245. A preponderance of the evidence supports this position. Petitioners brought J.T. to the doctor on August 31, 2012 because they were concerned about his development. Their concern with J.T. not sitting, not crawling, and not babbling were all skills that the pediatrician could observe and test. The fact that these skills were absent, and continued to be absent is significant. Indeed, Mr. Thompson noted that J.T. used to make attempts at crawling before his seizures, and then stopped. *See* Ex. 8 at 1403. However, Petitioners raised other concerns, both at this visit and at different medical appointments that were not typical developmental milestones. For example, the concern that J.T. was not able to finger feed is not something Dr. Fleischer was able to test and verify. Mrs. Thompson’s report that J.T. used to take a variety of foods before his first seizure, but as of January 4, 2013, he only preferred rice cereal was also not a typical developmental milestone measurable by J.T.’s pediatricians. Yet both of these documented concerns demonstrate that J.T. was either different or delayed after his first seizure on July 7, 2012. Also notable is the fact that several providers, one from a visit on January 4, 2013, and one from a visit on May 3, 2013, documented that J.T.’s development appeared to be at the six-month level. Ex. 8 at 1395; Ex. 8 at 1391. These observations support Petitioners’ contentions that J.T.’s first seizure at six months of age adversely impacted him. Petitioners have preponderantly established that J.T. experienced a stagnation in development which began after his first seizure on July 7, 2012.

### c. *Treating Physicians*

In weighing evidence, special masters are expected to consider the views of treating doctors. *Capizzano*, 440 F.3d at 1326. The views of treating doctors about the appropriate diagnosis are often persuasive because the doctors have direct experience with the patient whom they are diagnosing. *See McCulloch v. Sec'y of Health & Hum. Servs.*, No. 09-293V, 2015 WL 3640610, at \*20 (Fed. Cl. Spec. Mstr. May 22, 2015).

Dr. Orrin Devinsky is the Director of the NYU Comprehensive Epilepsy Center, the Director of the Saint Barnabas Institute of Neurology and Neurosurgery, and an attending physician in neurology at Tisch Hospital in New York. Devinsky CV at 1. Dr. Devinsky was also J.T.’s treating physician. Dr. Devinsky provided his opinion that “there is extremely strong evidence that [J.T.]’s epilepsy was activated by the third DT/DTaP vaccination on July 7, 2012.” Ex. 24. Although Dr. Devinsky did not provide a lengthy opinion or include a causation theory in

his letter, I have still considered his opinion and have found it persuasive in establishing that the DTaP vaccine “did cause” J.T.’s condition.<sup>9</sup>

*d. J.T.’s Developmental Plateauing Began at an Earlier Age than is Described in the Medical Literature*

In the preceding section, I found preponderant evidence supports the fact that J.T.’s plateauing began before his August 31, 2012 developmental appointment, or before he was eight months of age. The medical literature filed in this case consistently states that developmental plateauing or regression begins in the second year of life. For example, McIntosh et al. noted, “From the second year of life, intellectual development in these infants begins to plateau or regress, resulting in intellectual disability.” McIntosh at 592. C. Dravet stated, “As a rule, children start walking at a normal age but an unsteady gait develops for an unusually long period. Language also starts at a normal age, but progresses very slowly, and many patients do not reach the stage of constructing elementary sentences.” C. Dravet at 4. J.T. did not start walking or develop language on schedule. Claes et al. stated that “Early psychomotor and speech development is normal, but developmental stagnation occurs during the second year of life.” Claes et al., *De Novo Mutations in the Sodium-Channel Gene SCN1A Cause Severe Myoclonic Epilepsy of Infancy*, 68 AM. J. HUM. GENET., 1327–32 (2001) (filed as Ex. F2).

Verbeek et al. also described disease progression in children with Dravet syndrome.

**Table 2** Disease progression in children who had DS with and without vaccination-associated seizure onset

	Children with DS		First seizure not vaccination-associated (n = 61, 79%)	No. available	p Value
	First seizure vaccination-associated (n = 16, 21%)	No. available			
<b>Event, median age (range), mo</b>					
First seizure	3.7 (2.0–4.9)	16	6.1 (0.8–12)	61	<0.001 <sup>a</sup>
First nonvaccination-associated seizure	5.5 (3.6–9.0)	15	6.1 (0.8–12)	61	0.449
Start of AED treatment	6.1 (3.4–15)	16	9.1 (2.6–25)	61	0.008 <sup>a</sup>
First developmental delay reported in medical files	23 (16–52)	15	24 (6–68)	57	0.939
First developmental delay noticed by parents	24 (6–84)	15	21 (6–72)	53	0.688
<b>Outcome of children with DS, n (%)</b>					
Subsequent vaccination-associated seizures	11 (69)	16	26 (44)	59	0.08
Cognitive, IQ <50	11 (73)	15	34 (59) <sup>b</sup>	58	0.379
Deceased <sup>c</sup>	0 (0)	16	3 (5)	61	1.00

Abbreviations: AED = antiepileptic drug; DS = Dravet syndrome.

<sup>a</sup> Significant values.

<sup>b</sup> IQ <50 in 16 of 26 (62%) of those with and 16 of 30 (53%) of those without subsequent vaccination-associated seizures; p = 0.536, χ<sup>2</sup> test.

<sup>c</sup> Causes of death: status epilepticus (n = 1), sudden unexpected death in epilepsy (n = 2).

<sup>9</sup> I have also considered Dr. Thio’s opinion that “vaccinations probably did not have a causative role in [J.T.’s] epilepsy” in arriving at my determination that the Pentacel vaccine “did cause” a significant aggravation of his condition. Ex. 43 at 26.

Verbeek at 599. Verbeek documented that the first developmental delay in children with Dravet syndrome was noticed by parents at an average age of 24 months in children who experienced a vaccine-associated seizure, and at 21 months in children whose initial seizure was not associated with a vaccine. *Id.* Petitioners first expressed concern with J.T.’s development when he was eight months old. Similarly, Verbeek documented that the first developmental delay reported in the medical files was at 23 months in children who experienced a vaccine-associated seizure, and at 24 months in children whose initial seizure was not associated with a vaccine. *Id.* On November 9, 2012, Dr. Thio noted that J.T. had “mild axial and appendicular hypotonia.” Ex. 8 at 1403. J.T. was slightly over 10 months of age at this appointment. The fact that J.T.’s development was noticeably abnormal at a much earlier age than the cases of Dravet syndrome described in the medical literature supports Petitioners’ position that the DTaP component of the Pentacel vaccine “did cause” a significant aggravation of his condition.

In summary, Petitioners have established that J.T. suffered a febrile seizure between six and eight hours after his Pentacel vaccine on July 7, 2012. Preponderant evidence supports the fact that J.T.’s vaccination caused his febrile seizure. After this initial seizure and before his subsequent seizures on September 11, 2012, J.T.’s development began to plateau, consistent with Petitioners’ theory that the July 7, 2012 seizure damaged his brain. The medical literature demonstrates that children with Dravet syndrome have a plateauing or regression in development at a significantly older age than J.T. experienced. Finally, one of J.T.’s treating neurologists has opined that the DTaP vaccine activated J.T.’s epilepsy. Based on the above, I find that Petitioners have presented preponderant evidence in support of the fifth *Loving*/second *Althen* prong.

#### 6. *Loving* Prong Six/*Althen* Prong Three

The final *Loving* prong requires Petitioners to establish a “proximate temporal relationship” between the significant aggravation of J.T.’s condition and the vaccines he received. *Loving* at 144; *see also Althen*, 418 F.3d at 1281. Petitioners must offer “preponderant proof that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder’s etiology, it is medically acceptable to infer causation.” *de Bazan v. Sec’y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008).

The timing prong contains two parts. First, Petitioners must establish the “timeframe for which it is medically acceptable to infer causation” and second, they must demonstrate that the onset of the disease’s significant aggravation occurred in this period. *Shapiro v. Sec’y of Health & Hum. Servs.*, 101 Fed. Cl. 532, 542-43 (2011), *recons. denied after remand on other grounds*, 105 Fed. Cl. 353 (2012), *aff’d without op.*, 503 F. App’x 952 (Fed. Cir. 2013).

Petitioners have preponderantly established that J.T. suffered a vaccine-induced febrile seizure on July 7, 2012. The Sun article demonstrates that there is an increased risk of febrile seizures on the day of DTaP vaccination. Sun at 4-5. Dr. MacGinnitie also testified that this is the case (Tr. at 278), as did Dr. Shafrir. Tr. at 243. Taken together, this constitutes preponderant evidence that the timing of J.T.’s vaccine reaction, between six to eight hours after DTaP vaccination, is medically appropriate. Petitioners have presented preponderant evidence in support of the sixth *Loving*/third *Althen* prong.

### C. Alternate Causation

Petitioners have presented preponderant evidence in support of each of the *Loving* prongs. Once petitioners make a *prima facie* showing of causation, “the burden shifts to respondent to demonstrate by a preponderance of the evidence that a ‘factor unrelated’ to the vaccine ‘was the sole substantial factor in bringing about the injury.’” *Hammitt v. Sec'y of Health & Hum. Servs.*, 98 Fed. Cl. 719, 726 (2011), *aff'd sub nom. Stone v. Sec'y of Health & Hum. Servs.*, 676 F.3d 1373 (Fed. Cir. 2012) (citing *Bazan*, 539 F.3d at 1352).

Respondent contends that J.T.’s “EIEE19 consistent with DS is solely the result of his GABRA1 variant.” Resp’t’s Brief at 43. In order to analyze Respondent’s claim that a factor unrelated to vaccination was the sole substantial cause of J.T.’s injury, it is appropriate to evaluate the claim pursuant to an *Althen* analysis.

#### 1. *Althen* Prong One: J.T.’s GABRA1 Variant Can Cause Dravet Syndrome

Respondent has provided both the testimony of Dr. Raymond and medical literature which establishes that the GABRA1 variant can cause Dravet syndrome. Dr. Raymond testified to this point at the hearing, noting that GABRA1 gene variants have been associated with juvenile myoclonic epilepsy, idiopathic generalized epilepsy, and a subgroup of epileptic encephalopathies. Tr. at 310-11. He ultimately opined that the L215V missense mutation in J.T.’s GABRA1 gene caused him to develop EIEE19. Second Raymond Rep. at 11; Tr. at 362. Dr. Shafrir agreed that J.T.’s variant is pathogenic. Tr. at 47. Accordingly, this issue is uncontested. Respondent has preponderantly established that J.T.’s GABRA1 variant can cause Dravet syndrome.

#### 2. *Althen* Prong Two: There is not Preponderant Evidence that J.T.’s GABRA1 Variant Was the Sole Substantial Factor that Did Cause him to Develop Dravet Syndrome

Dr. Raymond opined that J.T.’s GABRA1 variant was the cause of his DS and that the vaccination played no role. As support for this position, Dr. Raymond noted that J.T.’s GABRA1 variant arose *de novo*, meaning that it was not inherited from his parents. Further, the variant arose in a functionally important region that is conserved across species, lending additional support to the importance of the variant in J.T.’s disease course. Additionally, Dr. Raymond testified that “variations in these regions generally … reveal themselves as a seizure disorder.” Tr. at 316.

Dr. Raymond testified that mutations in the GABRA1 gene do result in a variety of phenotypes, but stated that these varied presentations are a result of the “severity of the variation in the gene.” Tr. at 365.

Dr. Raymond discussed literature which demonstrates that position 214, next to 215 which is J.T.’s mutation on the GABRA1 gene, is also associated with EIEE19. Tr. at 332, referencing Ex. 117.

Dr. Raymond also highlighted exhibit K13 (excerpts from ClinVar)<sup>10</sup> in support of his position that an amino acid substituted at position 215 results in EIEE19. Dr. Raymond testified it is clear “that the leucine is absolutely essential at that point. So any substitution outward of the leucine for anything else is well established now to be associated with EIEE19, which is what J.T.’s condition is.” Tr. at 320.

Petitioners contend the ClinVar data show that GABRA1 variants result in a spectrum of presentations from IGE to JME to EIEE19.<sup>11</sup> Pet’r’s’ Brief at 29; citing Exs. 116-121. This position is supported by the results of J.T.’s whole exome sequencing, which state that “[m]utations in the GABRA1 gene have been reported in association with juvenile myoclonic epilepsy (JME), childhood absence epilepsy (CAE), idiopathic generalized epilepsy and Dravet syndrome.” Ex. 10 at 26.

Dr. Shafrir further disagreed that J.T.’s genetic variant was the sole substantial cause of his condition, and opined that GABRA1 variants result in different phenotypes, suggesting that environment plays a role in outcome. In support of this position, Dr. Shafrir cited Wei. See Wei et al., *Ion Channel Genes and Epilepsy: Functional Alteration, Pathogenic Potential, and Mechanism of Epilepsy*, NEUROSCI. BULL., DOI 10.1007/s12264-017-0134-1 (2017) (filed as Ex. 57) (hereinafter “Wei”). According to Dr. Shafrir, Wei demonstrates that a child with the same variant as J.T. had idiopathic generalized epilepsy (IGE), a much less severe form of epilepsy than EIEE19. Tr. at 250. The applicable portion of table 6 in Wei shows the following:

**Table 6** Mutations of epilepsy-associated GABA<sub>A</sub> receptor genes and their functional effects.

Gene	Phenotype	Inheritance	Mutations	Functional alteration	Ref.
<i>GABRA1</i>	CAE	<i>de novo</i>	S326fsX328	Destructive, LOF	[129]
	JME	AD	F104C, A322D	pLOF	[128, 130]
		Unknown	c.-248+1 G>T	Destructive	
	GEFS+	Paternal†	V74I	Not available	
	IGE	AD	D219N	pLOF	[134]
			K353delins18X	Destructive, LOF	[134]
		Maternal†	c.256-8 T>G	Destructive	
		Unknown	T20I, L215V, D219N	Not available	
			K306T	pLOF	[130]
MAE	de novo		S76R, G251S, K306T	pLOF	[130, 132]
			R112Q, L146M, R214H, T292I	Not available	
	EE	<i>de novo</i>	S76R, R214H	pLOF	[130]
			R112Q, N115D, G251D, P260L, M263I, M263T, V287L, T289P	Not available	
			K401fsX25	Destructive	
		Unknown	T289A	Not available	

Wei at 12. J.T.’s variant, L215V, resulted in a phenotype of idiopathic generalized epilepsy. Dr. Shafrir described this as “much milder than JT’s EIEE19 and typically not disabling.” Fourth

<sup>10</sup> ClinVar is “an archival database that aggregates information about genomic variation and its relationship to human health.” Ex. M1 at 1.

<sup>11</sup> Respondent stated that “Dr. Shafrir’s reliance upon these other ostensibly benign variants is wholly misplaced. This is because ClinVar is a ‘submission-driven database,’ which contains ‘both primary submissions as well as expert curated submissions.’ Tr. at 326. Consequently, ‘anyone can go into ClinVar and upload a variant[.]’” Respt’s Brief at 47-48.

Shafrir Rep. at 20. In response, Dr. Raymond testified that in retrieving close to 1,000 epilepsy-associated genes, Wei likely miscategorized this particular variant as resulting in IGE. Tr. at 343-44. He opined that there is no source listed for the L215V variant, which also makes Wei's data less reliable. *Id.*

Although both Petitioners and Respondent cited medical literature in support of their respective positions, both experts agreed that we know very little about J.T.'s variant, L215V. In one of his expert reports filed before the hearing, Dr. Raymond noted that “[t]here have been no functional studies of this variant.” First Raymond Rep. at 7. During the entitlement hearing, Dr. Raymond testified that we are not able to say what is a “typical” level of severity experienced by individuals with J.T.’s genetic variant. He stated: “we can talk about the spectrum of EIEE19, but I cannot specifically point you to a literature or an experience out there … for this particular variant in EIEE19.” Tr. at 386-87.

Indeed, in discussing the GABRA1 variant generally, Carvill stated that “[t]here is no clear genotype-phenotype correlation with respect to either nature or localization of the mutation and severity of phenotype.” Carvill at 1249. Further, there is no medical literature on GABRA1-associated epileptic encephalopathies and vaccinations. Tr. at 74; Third Shafrir Rep. at 7.

Perhaps to bridge this gap, the experts spent a great deal of time discussing the SCN1A variant. Special masters have adjudicated a number of SCN1A-Dravet syndrome cases, and all have been resolved against petitioners. *See, e.g., Oliver v. Sec'y of Health & Hum. Servs.*, No. 10-394V, 2017 WL 747846, at \*2 (Fed. Cl. Spec. Mstr. Feb. 1, 2017), *mot. for rev. den'd*, 133 Fed. Cl. 341, 344 (2017), *aff'd*, 900 F.3d 1357 (Fed. Cir. 2019); *Barnette ex rel. Barnette v. Sec'y of Health & Hum. Servs.*, No. 06-868V, 2012 WL 5285414, at \*4 (Fed. Cl. Spec. Mstr. Sept. 26, 2012), *mot. for rev. den'd, decision aff'd sub nom.*, 110 Fed. Cl. 34 (2013); *Stone v. Sec'y of Health & Hum. Servs.*, 2010 WL 1848220, No. 04-1041V (Fed. Cl. Spec. Mstr. Apr. 15, 2010), *mot. for rev. den'd*, 99 Fed. Cl. 187 (2011), *aff'd*, 676 F.3d at 1373 (Fed. Cir. 2012); *Deribeaux v. Sec'y of Health & Hum. Servs.*, No. 05-306V, 2011 WL 6935504, at \*32 (Fed. Cl. Spec. Mstr. Dec. 9, 2011), *mot. for rev. den'd*, 105 Fed. Cl. 583 (2012), *aff'd*, 717 F.3d 1363 (Fed. Cir. 2013). The outcome of these cases is in part due to studies like McIntosh, which concluded that although vaccination causes DS to begin months sooner than it ordinarily would have, this earlier onset does not alter developmental outcome. I note that the Cetica article was published in March of 2017, after many of these SCN1A-Dravet syndrome cases were decided. Cetica et al. concluded as follows: “In individuals with SCN1A mutations, age at seizure onset appears to predict outcome better than mutation type. Because outcome is not predetermined by genetic factors only, early recognition and treatment that mitigates prolonged/repeated seizures in the first year of life might also limit the progression to epileptic encephalopathy.” Cetica at 1.

Ultimately, however, it is not appropriate to apply the findings from McIntosh or other SCN1A studies to this case. First, the authors themselves caution that their “findings might not apply to the 20–30% of patients with Dravet syndrome who do not have SCN1A mutations.” McIntosh at 597. Additionally, I asked Dr. Raymond whether the SCN1A studies should be applied to a case involving a GABRA1 variant. Dr. Raymond testified as follows:

I really don't think we should be making that extrapolation. The SCN1A ... is a different variation. It has differing effects on the brain ... and so I think when you start to make these kinds of extrapolations, except in very broad strokes, you're going to be wrong. And so I am very hesitant ... to go down a path discussing SCN1A as being at all pertinent to this individual.

Tr. at 387. Accordingly, I cannot assume that developmental outcome in DS cases associated with a GABRA1 variant is not impacted by earlier onset of seizures, as there are no studies in support of this position. *See Sanchez v. Sec'y of Health & Hum. Servs.*, 34 F.4th 1350, 1356 (Fed. Cir. 2022) (finding respondent's alternate causation argument unpersuasive in part due to the lack of evidence that the minor child's genetic mutation "would have resulted in the same [disease] progression and severity ... absent the vaccine.").

At the end of the analysis, what remains is a genetic variant to which we are unable to ascribe a typical level of severity, along with a complete absence of medical literature on GABRA1-associated epileptic encephalopathies and vaccination. With this backdrop, I am unable to conclude that J.T.'s GABRA1 variant, more likely than not, was the sole substantial cause of his condition. This is especially true given my findings in section VI(B)(5) that J.T. experienced a seizure caused by his DTaP vaccination followed by a developmental plateauing that began before his second seizure on September 11, 2012. *See Stone*, 2010 WL 1848220 at \*41 (ruling against petitioners in an SCN1A-Dravet syndrome case, the former Chief Special Master stated "[b]ased on the concessions made by Dr. Raymond,<sup>12</sup> the undersigned notes that if a similar case presented, but was one that demonstrated **evidence of brain injury** subsequent to a complex seizure caused by a postvaccination fever, the undersigned would be inclined to find the vaccine was a substantial factor contributing to the injury regardless of the nature of the gene mutation.") (emphasis in original). Such is my finding in the case at bar. Respondent has not established that J.T.'s GABRA1 variant was the sole substantial factor that "did cause" him to develop Dravet syndrome.

### 3. *Althen* Prong Three: J.T.'s Dravet Syndrome Developed in a Timeframe Consistent with his GABRA1 Variant being the Sole Substantial Cause of his Condition

J.T.'s initial seizure at six months of age marked the onset of his Dravet syndrome. The medical literature establishes that children with DS develop normally until they experience a seizure in the first year of life. McIntosh noted that Dravet syndrome "is characterised by onset of seizures at around 6 months of age." McIntosh at 592. Dr. Charlotte Dravet stated that onset of seizures occurs in the first year of life. C. Dravet at 1. Dr. Raymond testified that children typically experience seizures between six to twelve months of age. Tr. at 300. Accordingly, the fact that J.T. experienced his first seizure at six months of age is consistent with the medical literature filed into the record and the medical opinion provided at hearing. Respondent has preponderantly established

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<sup>12</sup> In *Stone*, Dr. Raymond testified that DTaP vaccination can cause a fever, and in some children, it can cause febrile seizures, "including complex febrile seizures." *Stone*, 2010 WL 1848220 at \*41. "[C]omplex febrile seizures are "seizures lasting longer than 15 minutes, occurring more than once in [ ] 24 hours, or having focal features." *Id.* at 10. Dr. Raymond further testified that a complex febrile seizure can injure the brain. *Id.* at 41.

that the onset of J.T.'s Dravet syndrome occurred in a medically appropriate timeframe to have been caused by his genetic variant.

While it is clear that J.T.'s GABRA1 variant led him to develop DS, Respondent has not preponderantly established that it was the sole substantial cause of his condition.

## **VII. Conclusion**

Upon careful evaluation of all the evidence submitted in this matter, including the medical records, the affidavits and testimony, as well as the experts' opinions and medical literature, I conclude that Petitioners have met their burden of proof under *Loving*. I further find that Respondent has not demonstrated that J.T.'s GABRA1 variant was the sole substantial factor in bringing about his EEIE19. Accordingly, Petitioners are entitled to compensation. An order regarding damages will issue shortly.

**IT IS SO ORDERED.**

s/ Katherine E. Oler  
Katherine E. Oler  
Special Master